EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2017
EMA/173251/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Synjardy

International non-proprietary name: empagliflozin / metformin

Procedure No. EMEA/H/C/003770/II/0015

Note

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

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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
HbA_{1c}	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 GmbH submitted to the European Medicines Agency on 3 February 2016 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

Extension of Indication to include treatment with Synjardy as adjunct to standard care therapy in adult patients with type 2 diabetes mellitus and high cardiovascular risk when treatment with empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the risk of all-cause mortality by reducing cardiovascular death and cardiovascular death or hospitalization for heart failure. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated based on the final CSR of study EMPA-REG OUTCOME. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections in the SmPC. Moreover, the updated RMP version 5.0 has been submitted.

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 P/271/2011 on the granting of a product-specific waiver.

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 were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	3 February 2016
Start of procedure:	27 February 2016
CHMP Rapporteur Assessment Report	12 April 2016
CHMP Co-Rapporteur Assessment Report	26 April 2016
PRAC Rapporteur Assessment Report	29 April 2016
PRAC members comments	3 May 2016
Updated PRAC Rapporteur Assessment Report	4 May 2016
PRAC Outcome	13 May 2016
CHMP members comments	17 May 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 May 2016
Request for supplementary information (RSI)	26 May 2016
Submission of MAHs responses	15 July 2016
CHMP Rapporteur Assessment Report	22 August 2016
PRAC Rapporteur Assessment Report	22 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	5 September 2016
Updated CHMP Rapporteur Assessment Report	9 September 2016
2nd Request for supplementary information (RSI)	15 September 2016
Request for clock stop extension dated	10 October 2016
Submission of MAH's responses	24 November 2016
CHMP Rapporteur Assessment Report	28 December 2016
PRAC Rapporteur Assessment Report	30 December 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	12 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur Assessment Report	19 January 2017
Opinion	26 January 2017

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. 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.

Metformin has been available for over 50 years and, together with lifestyle modification, is recommended by the American Diabetes Association and European Association for the Study of Diabetes as the first-line therapy for type 2 diabetes. Metformin lowers blood glucose levels primarily by suppressing hepatic gluconeogenesis. Metformin also improves insulin sensitivity of peripheral tissues and decreases gastrointestinal tract glucose absorption without exerting any direct effect on pancreatic β-cell insulin secretion. Through these mechanisms, metformin therapy typically leads to substantial improvements in glycaemic control but it does not promote weight gain or increase the risk of hypoglycaemia.

Synjardy is a twice-daily fixed dose combination of empagliflozin and immediate-release metformin that is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus. Synjardy was approved in the EU and the US in 2015, and has been submitted for approval in numerous other countries worldwide.

In this application, the proposed new indications 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 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 / metformin. Empagliflozin/ metformin 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 EmpaReg 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.

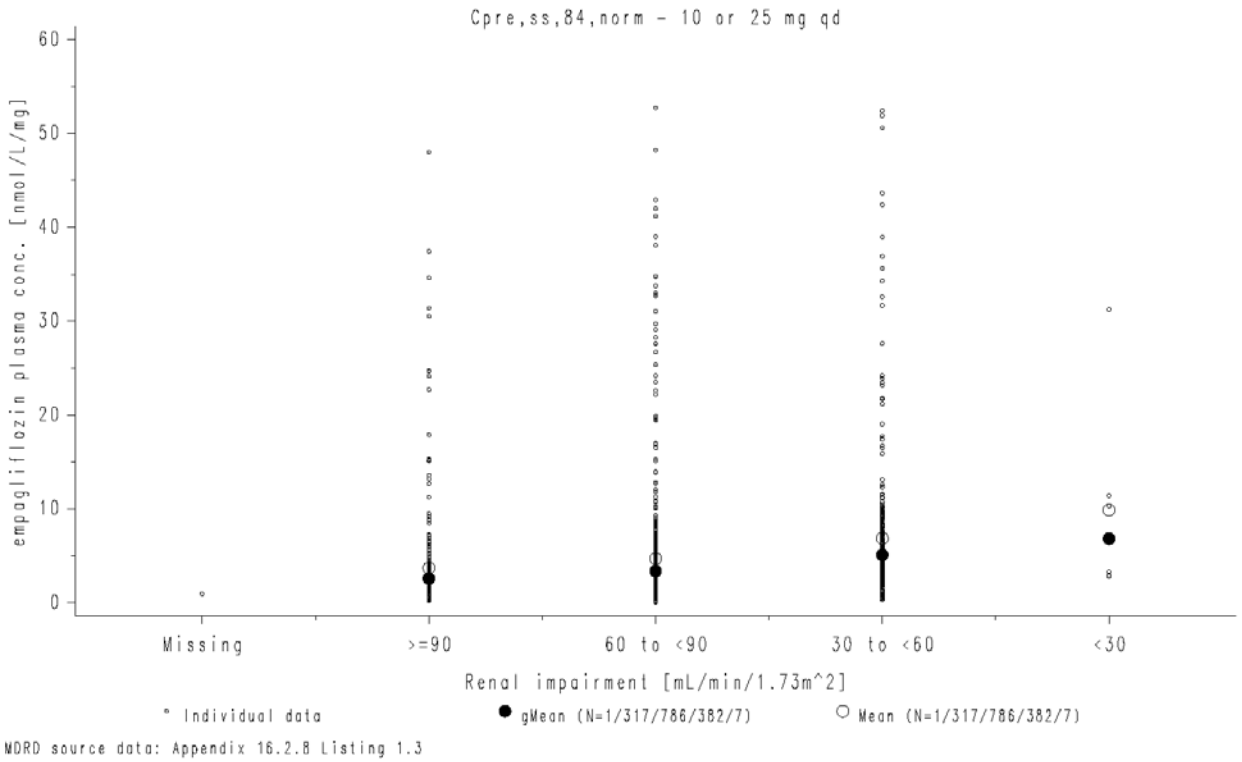

Figure 1 Comparison of dose normalised plasma through concentrations of empagliflozin after multiple oral administration in patients by renal impairment.

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 15 Summary of Efficacy for trial EMPA-REG.

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 Synjardy, subjects with moderate renal insufficiency (eGFR between 30 and 60 ml/min 1.73m^2) were fully eligible for all treatments.

In this document, the effect of empagliflozin vs. placebo as add-on to standard of care is compared (also) between the subgroup of patients taking metformin at baseline and the entire study population. This approach was chosen to check for consistency of the results in patients on a metformin background with the results of the entire trial population. All patients who received metformin background treatment at baseline were included irrespective of the metformin dose and any changes thereof after baseline.

The individual empagliflozin doses showed similar effects in the entire trial population and in the subgroup of patients receiving metformin at baseline; results for the individual dose groups are not discussed here. However, such results are shown in the AR of Jardiance for the entire trial population.

Treatments

Empagliflozin was administered in 10 mg or 25 mg doses once daily and compared to placebo. The study dose is in line with the current SmPC of Synjardy. Empagliflozin was administered once daily, whereas in Synjardy it is administered twice daily. This was addressed in the original MAA of Synjardy and found of no clinical relevance.

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. Metformin could be included in this background medication, thus enabling this discussion for Synjardy.

Of note, the trial included also patients with impaired renal function (eGFR < 60 ml/min/1.73m^2) for whom Synjardy is currently not authorized.

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 other secondary and further 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).

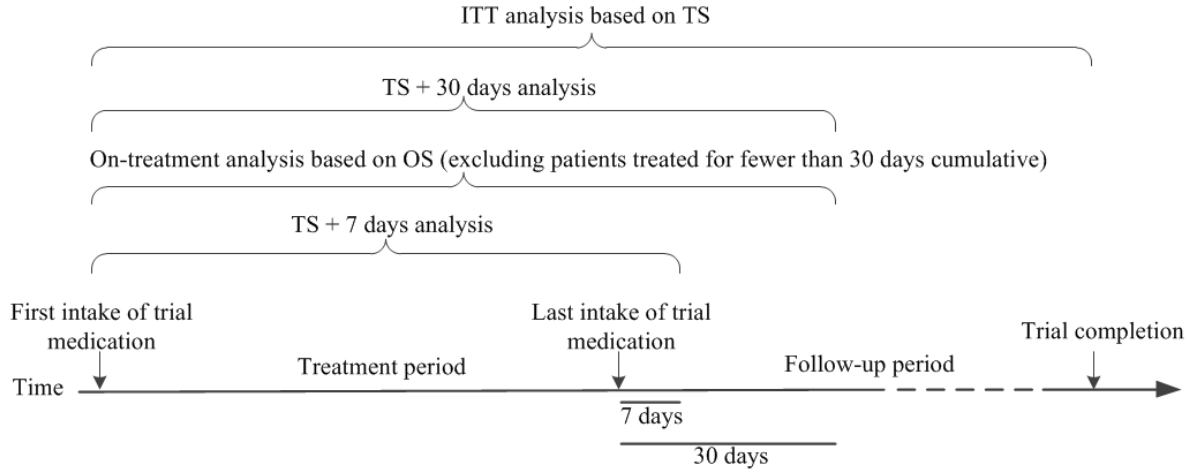

Figure 2 Illustration of the analyses based on the TS and OS

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 $\alpha=0.0001$ 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

(Table 1). 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%).

Table 1 Disposition of patients - screened set

	Patients on metformin at baseline					All patients				
	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Enrolled/screened patients					NA					11531
Patients who started placebo run-in period					NA					7610
Entered/randomised patients	1734	1729	1730	3459	5193	2337	2347	2344	4691	7028
Not treated patients	0	0	0	0	0	4	2	2	4	8
Treated patients	1734	1729	1730	3459	5193	2333	2345	2342	4687	7020
Prematurely discontinued trial[1]	46 (2.7)	61 (3.5)	48 (2.8)	109 (3.2)	155 (3.0)	67 (2.9)	81 (3.5)	63 (2.7)	144 (3.1)	211 (3.0)
Consent withdrawn	23 (1.3)	32 (1.9)	23 (1.3)	55 (1.6)	78 (1.5)	31 (1.3)	41 (1.7)	30 (1.3)	71 (1.5)	102 (1.5)
Site closure	14 (0.8)	21 (1.2)	19 (1.1)	40 (1.2)	54 (1.0)	25 (1.1)	30 (1.3)	26 (1.1)	56 (1.2)	81 (1.2)
Lost to follow-up for 3P-MACE	9 (0.5)	8 (0.5)	6 (0.3)	14 (0.4)	23 (0.4)	11 (0.5)	10 (0.4)	7 (0.3)	17 (0.4)	28 (0.4)
Prematurely discont trial med.	463 (26.7)	377 (21.8)	367 (21.2)	744 (21.5)	1207 (23.2)	683 (29.3)	555 (23.7)	542 (23.1)	1097 (23.4)	1780 (25.4)
Adverse event	195 (11.2)	177 (10.2)	180 (10.4)	357 (10.3)	552 (10.6)	303 (13.0)	267 (11.4)	273 (11.7)	540 (11.5)	843 (12.0)
Lack of efficacy[2]	11 (0.6)	0	0	0	11 (0.2)	11 (0.5)	1 (<0.1)	0	1 (<0.1)	12 (0.2)
Non-compliance with protocol	14 (0.8)	11 (0.6)	7 (0.4)	18 (0.5)	32 (0.6)	15 (0.6)	15 (0.6)	12 (0.5)	27 (0.6)	42 (0.6)
Lost to follow-up	10 (0.6)	7 (0.4)	5 (0.3)	12 (0.3)	22 (0.4)	15 (0.6)	9 (0.4)	6 (0.3)	15 (0.3)	30 (0.4)
Refused to continue trial med.[3]	121 (7.0)	84 (4.9)	88 (5.1)	172 (5.0)	293 (5.6)	172 (7.4)	118 (5.0)	122 (5.2)	240 (5.1)	412 (5.9)
Other reason	107 (6.2)	96 (5.6)	83 (4.8)	179 (5.2)	286 (5.5)	162 (6.9)	142 (6.1)	125 (5.3)	267 (5.7)	429 (6.1)
reason missing	5 (0.3)	2 (0.1)	4 (0.2)	6 (0.2)	11 (0.2)	5 (0.2)	3 (0.1)	4 (0.2)	7 (0.1)	12 (0.2)

NA = Not analysed

1 Follow-up information for 3-point MACE endpoint not available for entire trial period because of withdrawn consent, site closure (without transfer to another site) or being lost to follow-up for 3-point MACE for other reasons. For 161 of these 211 patients in the entire trial population, vital status information was available; thus, for 50 patients follow-up information was available neither for 3-point MACE nor for vital status. Among patients with metformin at baseline, vital status information was available for 122 of the 155 patients; thus, for 33 patients follow-up information was available neither for 3-point MACE nor for vital status.

2 Hyperglycaemia above protocol-defined level despite rescue therapy

3 Not due to adverse event

Recruitment

This trial was a multi-centre trial conducted globally. A total of 11 531 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 shown and no breakdown per group (Table 2).

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%).

Patients on metformin at baseline had similar demographics and baseline characteristics as the entire trial population. A small difference to the entire trial population was seen for renal function. Among the subgroup with metformin intake, more patients had normal renal function (metformin subgroup: 25.0%, overall: 21.9%) and fewer patients had moderate renal impairment than in the entire trial population (20.6% vs. 25.5%). This can be explained by the fact that in Europe (at the time of trial conduct) metformin had not been indicated in patients with a low creatinine clearance.

For patients using Synjardy, the daily metformin dose is 1700-2000 mg according to the SmPC. Among the patients with metformin background therapy at baseline, the median daily dose of metformin was 1700 mg (range 200 to 4250 mg/day). The daily metformin dose was below 1500 mg in 26.5% of patients (those with metformin), while it was at least 1700 mg in 65.5% of patients. The daily dose was >2000 mg in 21.0% of patients receiving metformin. Metformin doses at baseline were somewhat higher in the placebo group (median 2000 mg, mean 1768 mg) than in the empagliflozin groups (all empagliflozin: median 1700 mg, mean 1743 mg). More patients in the placebo group (16.7%) than in the empagliflozin groups (all empagliflozin: 8.8%) increased the metformin dose for at least 7 consecutive days during the treatment period. In contrast, decreases occurred at similar frequencies in all 3 treatment groups.

Table 2 Demographic and baseline data of the study population – TS

Variable	Category	Patients on metformin at baseline	All patients
Treated patients, N (%)		5193	7020
Sex, N (%)	Male	3720 (71.6)	5016 (71.5)
	Female	1473 (28.4)	2004 (28.5)
Race[1], N (%)	White	3737 (72.0)	5081 (72.4)
	Asian	1161 (22.4)	1517 (21.6)
	Black/African American	254 (4.9)	357 (5.1)
Region, N (%)	Europe	2106 (40.6)	2885 (41.1)
	North America	961 (18.5)	1394 (19.9)
	Asia	1030 (19.8)	1347 (19.2)
	Latin America	837 (16.1)	1081 (15.4)
	Africa	259 (5.0)	313 (4.5)
Age [years], mean (SD)		62.5 (8.6)	63.1 (8.6)
Age category, N (%)	<50 years	354 (6.8)	439 (6.3)
	50 to <65 years	2704 (52.1)	3454 (49.2)
	65 to <75 years	1731 (33.3)	2475 (35.3)
	≥75 years	404 (7.8)	652 (9.3)
Time since diagnosis of T2DM, N (%)	≤1 year	112 (2.2)	180 (2.6)
	>1 to 5 years	830 (16.0)	1083 (15.4)
	>5 to 10 years	1360 (26.2)	1746 (24.9)
	>10 years	2891 (55.7)	4011 (57.1)
eGFR (MDRD) category, N (%)	≥90 mL/min/1.73m^2	1299 (25.0)	1538 (21.9)
	60 to <90 mL/min/1.73m^2	2812 (54.1)	3661 (52.2)
	45 to <60 mL/min/1.73m^2	830 (16.0)	1249 (17.8)
	30 to <45 mL/min/1.73m^2	241 (4.6)	543 (7.7)
	<30 mL/min/1.73m^2	9 (0.2)	27 (0.4)
CV high-risk factor, N (%)	Any CV high-risk factor	5144 (99.1)	6964 (99.2)
	Coronary artery disease	3936 (75.8)	5308 (75.6)
	History of stroke	1179 (22.7)	1637 (23.3)
	Peripheral artery disease	1011 (19.5)	1461 (20.8)
HbA_{1c} [%], mean (SD)		8.06 (0.84)	8.07 (0.85)
FPG [mg/dL], mean (SD)		152.5 (41.9)	152.9 (43.8)
BMI [kg/m^2], mean (SD)		30.66 (5.19)	30.62 (5.26)
History of hypertension, N (%)		4722 (90.9)	6419 (91.4)
Blood pressure [mmHg], N (%)	SBP <140 and DBP <90	3180 (61.2)	4306 (61.3)
UACR category [mg/g], N (%)	Normal (<30)	3171 (61.1)	4171 (59.4)
	Microalbumin. (30 to 300)	1452 (28.0)	2013 (28.7)
	Macroalbuminuria (>300)	522 (10.1)	769 (11.0)
Medication use at baseline, N (%)	Any antidiabetic background medication	5193 (100.0)	6891 (98.2)
	Metformin	5193 (100.0)	5193 (74.0)
	Insulin	2184 (42.1)	3387 (48.2)
	Antihypertensives	4936 (95.1)	6667 (95.0)
	Anticoagulants	4634 (89.2)	6252 (89.1)
	Lipid-lowering drugs	4252 (81.9)	5684 (81.0)

Patients with missing information are not shown.

[1] In the entire trial population, 54 additional patients (0.8%) were American Indian/Alaska Native and 10 additional patients (0.1%) were native Hawaiian or other Pacific Islander.

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 Table 3. 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 3 Patient analysis sets (all patients)

	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.

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 4). The Kaplan-Meier estimates for time to first 3-point MACE are shown in **Figure 3 - Kaplan-Meier estimates of time to first 3-point MACE, all empagliflozin vs. placebo – TS (patients taking metformin; x-axis: study day)**.

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

	Patients on metformin at baseline		**All patients**	
	Placebo	**All empa**	**Placebo**	**All empa**
Analysed patients, N (%)	1734	3459	2333	4687
Patients with event, N (%)	189 (10.9)	344 (9.9)	282 (12.1)	490 (10.5)
Incidence rate per 1000 years at risk	38.9	35.3	43.9	37.4
Hazard ratio vs. placebo	–	0.92	–	0.86
95% CI[1]	–	(0.77, 1.10)	–	(0.74, 0.99)

[1] Note that the primary analysis for the entire trial population employed a 95.02% CI based on the reduced alpha level of 0.0249 resulting from the interim analysis. The 95.02% CI was 0.74 to 0.99 (same as the 95% CI) leading to the conclusion of superiority of empagliflozin over placebo (2-sided p-value 0.0382).
Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.1378

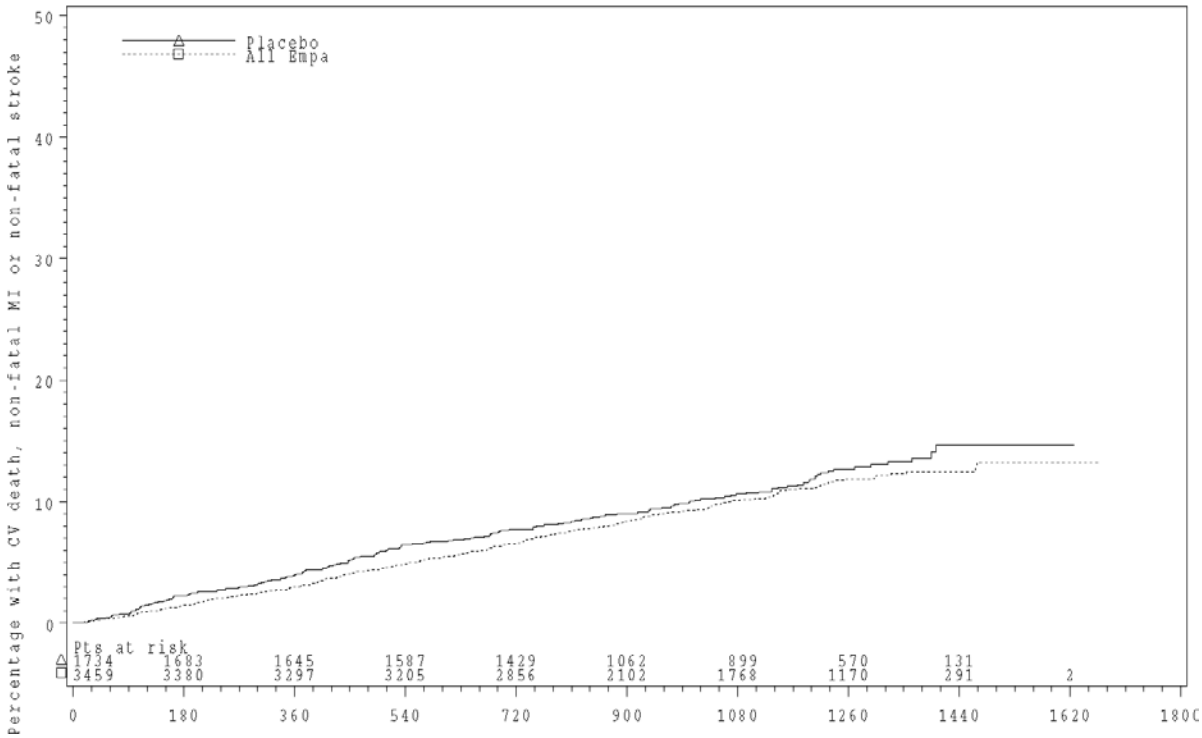

Figure 3 - Kaplan-Meier estimates of time to first 3-point MACE, all empagliflozin vs. placebo – TS (patients taking metformin; x-axis: study day)

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.

The breakdown of the first event for 3-point MACE indicated that the somewhat lower frequency of 3-point MACE for empagliflozin was primarily due to the lower frequency of CV death (Table 5). 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 Breakdown of the first event for 3-point MACE (TS)

	Patients on metformin at baseline		**All patients**	
	Placebo N (%)	**All empa N (%)**	**Placebo N (%)**	**All empa N (%)**
Analysed patients	1734	3459	2333	4687
Patients with confirmed event	189 (10.9)	344 (9.9)	282 (12.1)	490 (10.5)
CV death	67 (3.9)	97 (2.8)	107 (4.6)	143 (3.1)
Non-fatal MI	81 (4.7)	149 (4.3)	120 (5.1)	208 (4.4)
Non-fatal stroke	41 (2.4)	100 (2.9)	55 (2.4)	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 AR for Jardiance. The results for subgroups show good consistency with the overall primary endpoint and are not repeated here for brevity.

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 6 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. Also in metformin users, the results were similar (placebo: 48 (2.8%), all empa 91 (2.6%)).

Table 6 Cox regression for time to first 4-point MACE, empagliflozin vs. placebo – TS

	Patients on metformin at baseline		All patients	
	Placebo	All empa	Placebo	All empa
Analysed patients, N (%)	1734	3459	2333	4687
Patients with event, N (%)	230 (13.3)	427 (12.3)	333 (14.3)	599 (12.8)
Incidence rate per 1000 years at risk	48.1	44.6	52.5	46.4
Hazard ratio vs. placebo	–	0.94	–	0.89
95% CI[1]	–	(0.80, 1.10)	–	(0.78, 1.01)

[1] Note that the main analysis for the entire trial population employed a 95.02% CI based on the reduced alpha level of 0.0249 resulting from the interim analysis. The 95.02% CI was 0.78 to 1.01 (same as the 95% CI) leading to the conclusion that empagliflozin was not superior to placebo (2-sided p-value 0.0795).
Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.2077

Component: CV death (and all-cause mortality)

The risk of CV death and all-cause mortality was significantly reduced in the "all empagliflozin" group (all users) 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 group compared with the placebo group (Table 7 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 7 Summary of endpoints of death – TS

	Patients on metformin at baseline		All patients	
	Placebo	**All empa**	**Placebo**	**All empa**
Analysed patients (TS), N (100%)	1734	3459	2333	4687
All-cause mortality				
Patients with event, N (%)	115 (6.6)	176 (5.1)	194 (8.3)	269 (5.7)
Incidence rate per 1000 years at risk	22.5	17.1	28.6	19.4
Hazard ratio vs. placebo (95% CI)	–	0.78 (0.61, 0.98)	–	0.68 (0.57, 0.82)
CV death				
Patients with event, N (%)	84 (4.8)	118 (3.4)	137 (5.9)	172 (3.7)
Incidence rate per 1000 years at risk	16.4	11.5	20.2	12.4
Hazard ratio vs. placebo (95% CI)	–	0.71 (0.54, 0.94)	–	0.62 (0.49, 0.77)

Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.0576 (all-cause mortality), p = 0.0743 (CV death)

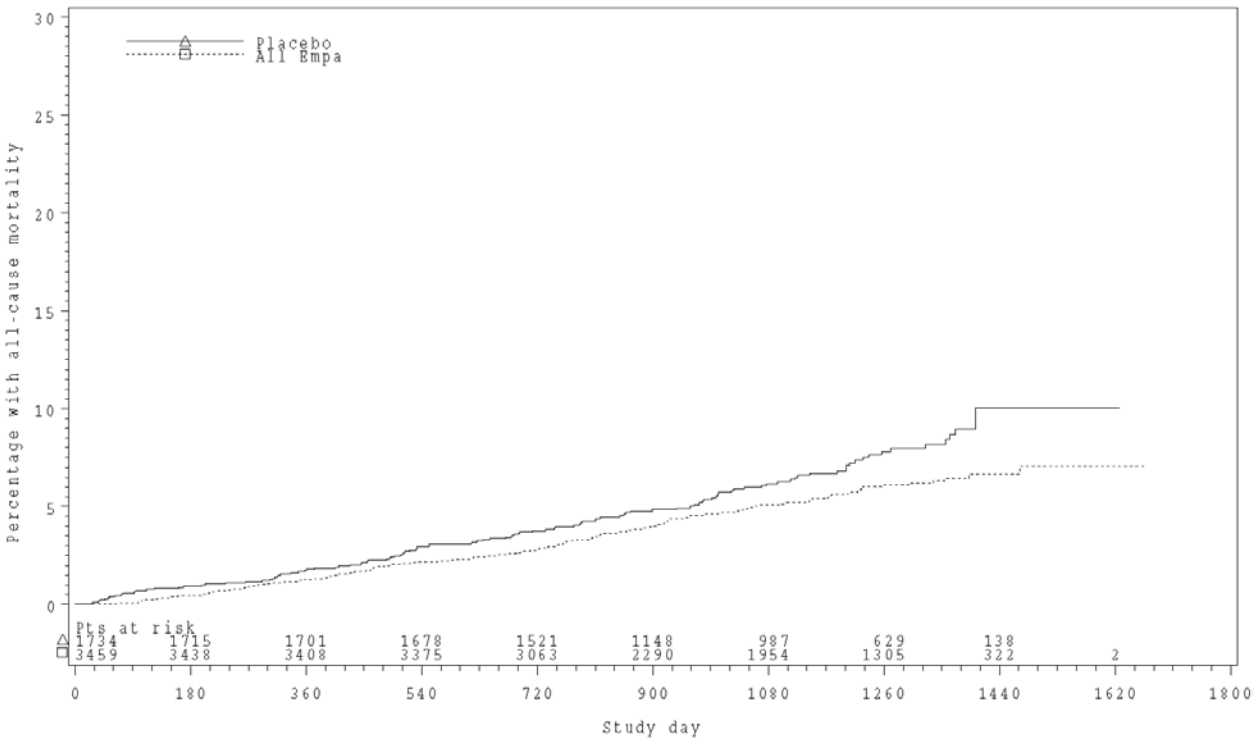

Figure 4 Kaplan-Meier estimates of time to all-cause mortality, all empagliflozin vs. placebo – TS (metformin at baseline)

Component: Myocardial infarction (MI)-related outcomes

For all MI-related endpoints, no significant difference was observed between empagliflozin and placebo (Table 8).

Table 8 Summary of MI-related endpoints - TS

	Patients on metformin at baseline		All patients	
	Placebo	All empa	Placebo	All empa
MI (fatal/non-fatal)[1]				
Analysed patients (TS), N (100%)	1734	3459	2333	4687
Patients with event, N (%)	84 (4.8)	158 (4.6)	126 (5.4)	223 (4.8)
Incidence rate per 1000 years at risk	17.0	16.0	19.3	16.8
Hazard ratio vs. placebo (95% CI)	-	0.95 (0.73, 1.24)	-	0.87 (0.70, 1.09)
Non-fatal MI[2]				
Analysed patients (TS), N (100%)	1734	3459	2333	4687
Patients with event, N (%)	81 (4.7)	153 (4.4)	121 (5.2)	213 (4.5)
Incidence rate per 1000 years at risk	16.4	15.5	18.5	16.0
Hazard ratio vs. placebo (95% CI)	-	0.96 (0.73, 1.25)	-	0.87 (0.70, 1.09)

MI excludes silent MI unless these events were reported by investigators and confirmed as MI by central adjudication committee. .

[1] Treatment by metformin at baseline interaction for all empagliflozin versus placebo: p = 0.2224

[2] Treatment by metformin at baseline interaction for all empagliflozin versus placebo: p = 0.1845

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 9). Strokes were classified into ischaemic, haemorrhagic, and type not assessable by the CEC neurology. The majority of confirmed strokes were ischaemic.

Table 9 Summary of cerebrovascular disease-related endpoints - TS

	Patients on metformin at baseline		All patients	
	Placebo	All empa	Placebo	All empa
Stroke (fatal/non-fatal)[1]				
Analysed patients, N (100%)	1734	3459	2333	4687
Patients with event, N (%)	48 (2.8)	117 (3.4)	69 (3.0)	164 (3.5)
Incidence rate per 1000 years at risk	9.7	11.8	10.5	12.3
Hazard ratio vs. placebo (95% CI)	-	1.23 (0.88, 1.73)	-	1.18 (0.89, 1.56)
Non-fatal stroke[2]				
Analysed patients, N (100%)	1734	3459	2333	4687
Patients with event, N (%)	44 (2.5)	105 (3.0)	60 (2.6)	150 (3.2)
Incidence rate per 1000 years at risk	8.9	10.6	9.1	11.2
Hazard ratio vs. placebo (95% CI)	-	1.21 (0.85, 1.71)	-	1.24 (0.92, 1.67)

1 Treatment by metformin at baseline interaction for all empagliflozin versus placebo: p = 0.6013

2 Treatment by metformin at baseline interaction for all empagliflozin versus placebo: p = 0.7909

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 5). For patients in Europe, the differences are larger and the separation appears earlier (around Day 180) for both doses (Figure 6).

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 6). 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.

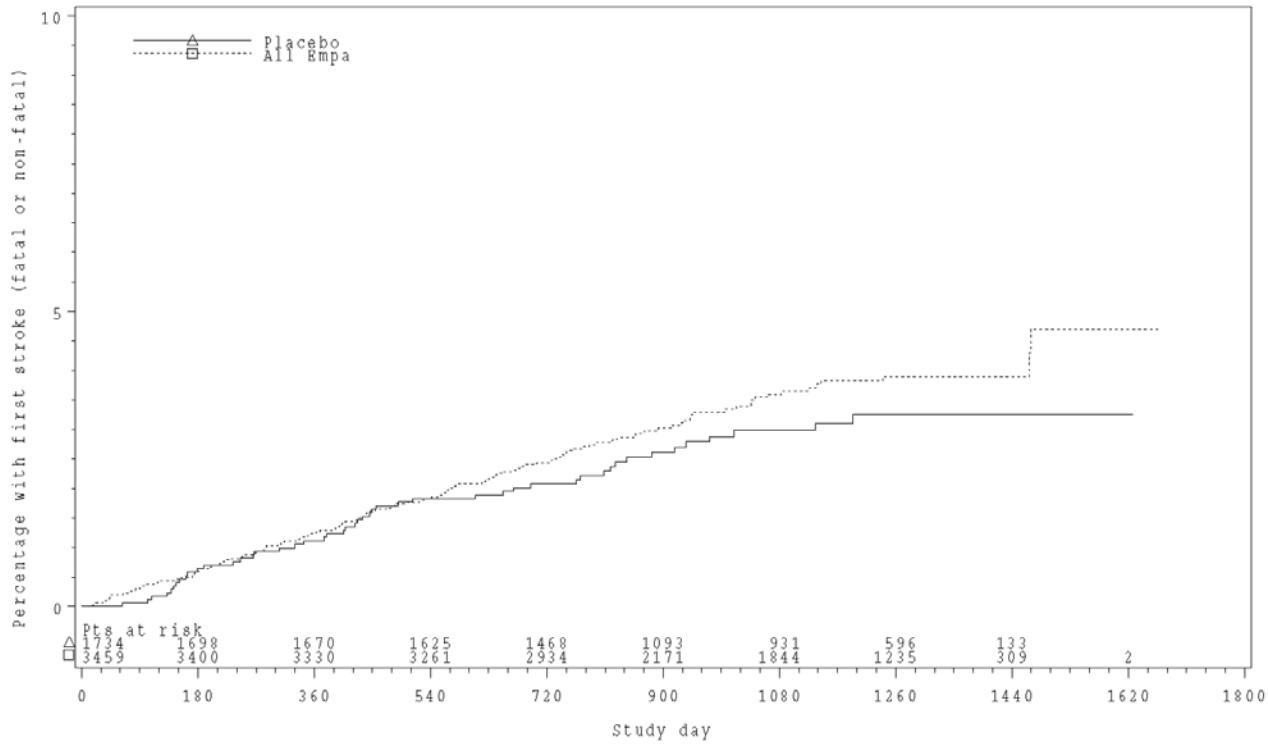

Figure 5 Time to first stroke (TS – patients at baseline on metformin)

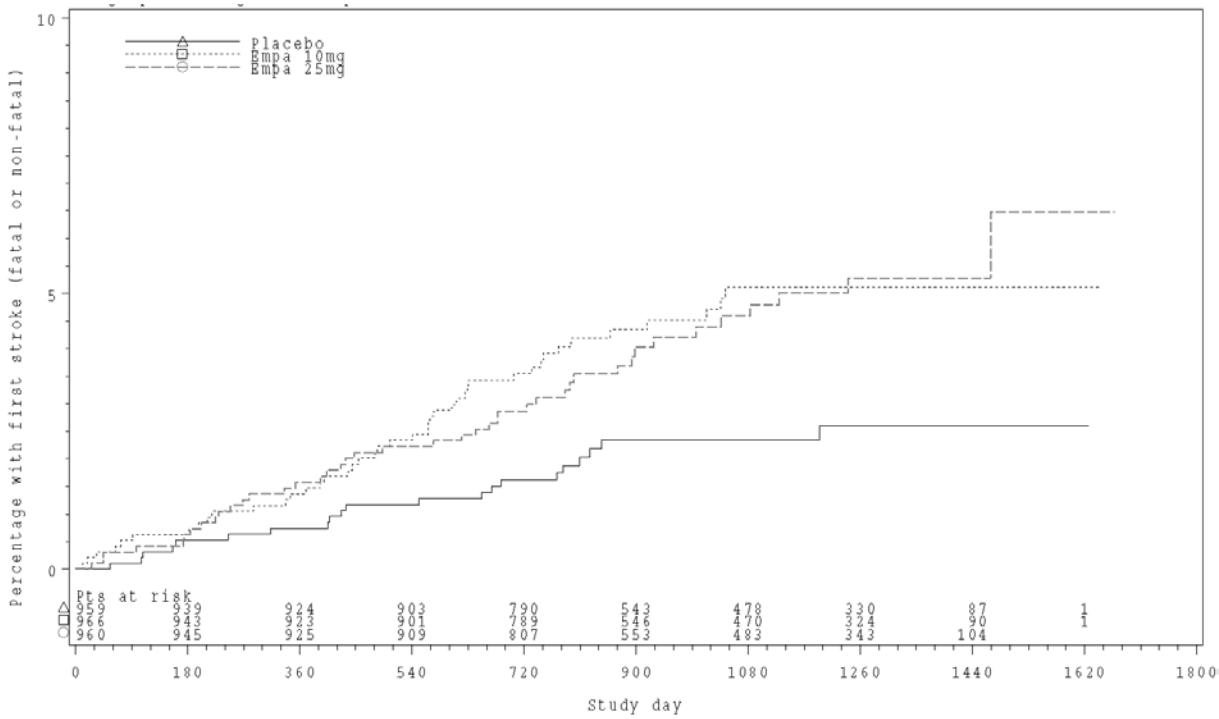

Figure 6 Time to first stroke in Europe.

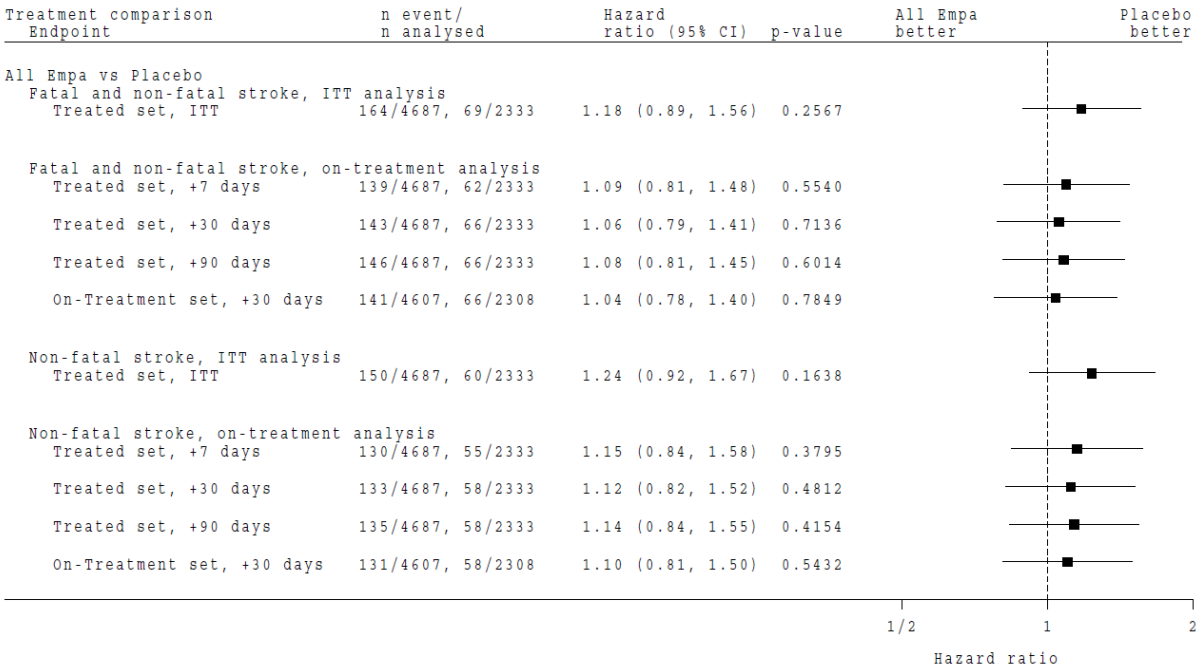

Figure 7 Overview of Cox regression analyses for stroke and non-fatal stroke, all empagliflozin vs. placebo

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 (Table 10). 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 10 Summary of heart failure-related endpoints – TS

	Patients on metformin at baseline		All patients	
	Placebo	**All empa**	**Placebo**	**All empa**
Analysed patients (TS), N (100%)	1734	3459	2333	4687
Heart failure requiring hospitalisation				
Patients with event, N (%)	59 (3.4)	79 (2.3)	95 (4.1)	126 (2.7)
Incidence rate per 1000 years at risk	11.9	7.9	14.5	9.4
Hazard ratio vs. placebo (95% CI)	–	0.68 (0.49, 0.95)	–	0.65 (0.50, 0.85)
Heart failure requiring hospitalisation or CV death (excl. fatal stroke)				
Patients with event, N (%)	123 (7.1)	173 (5.0)	198 (8.5)	265 (5.7)
Incidence rate per 1000 years at risk	24.7	17.3	30.1	19.7
Hazard ratio vs. placebo (95% CI)	–	0.71 (0.57, 0.90)	–	0.66 (0.55, 0.79)

Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.6112 (heart failure req. hospitalisation), p = 0.1769 (heart failure req. hospitalisation or CV death excluding fatal stroke)

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 (

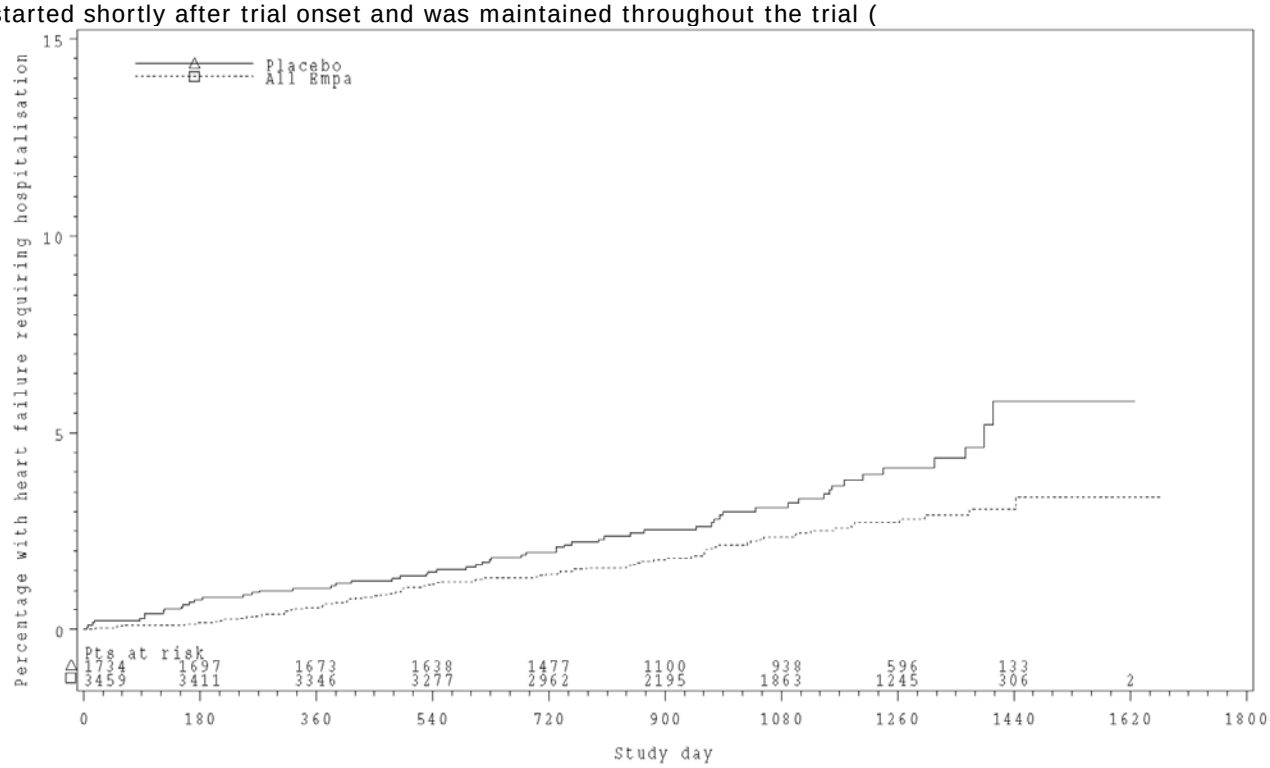

Figure 8)

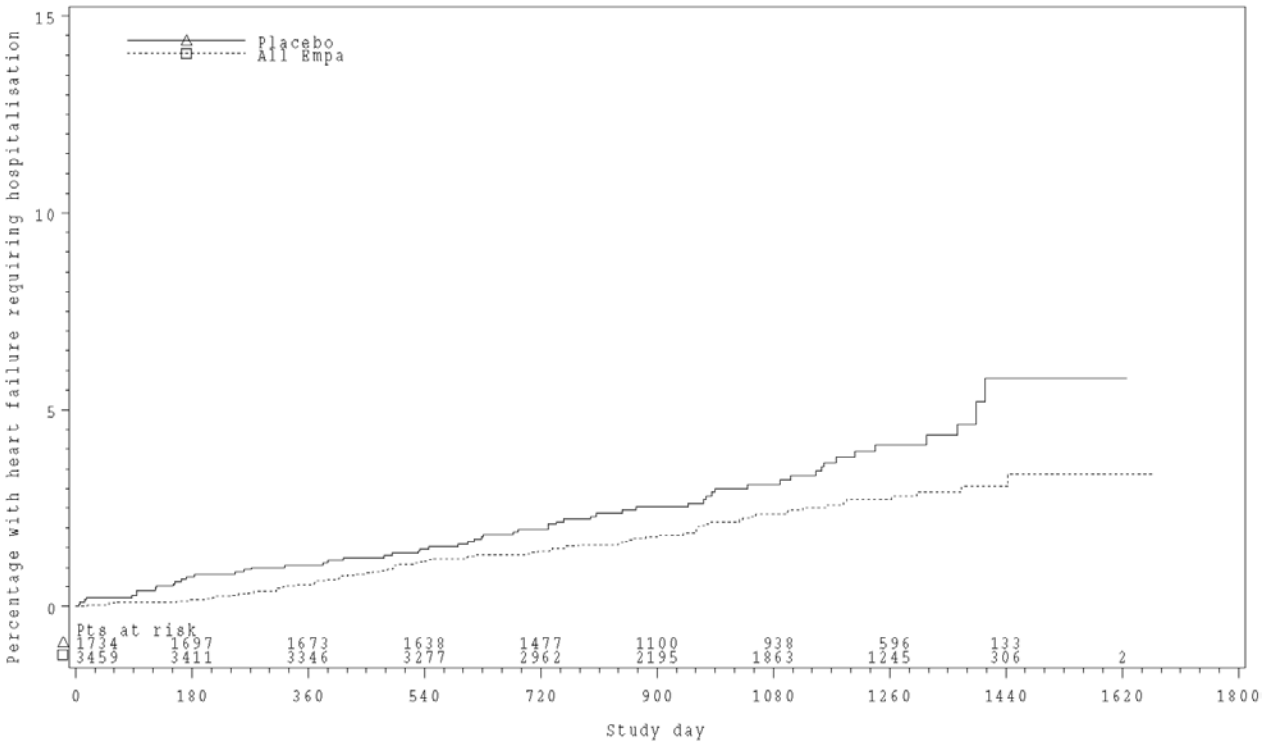

Figure 8 Kaplan-Meier estimates of time to heart failure requiring hospitalisation, all empagliflozin vs. placebo – TS (patients with metformin at baseline)

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). 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 compared with the

placebo group (Table 11). The Kaplan-Meier estimation of cumulative probability of events are shown in Figure 8. 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 11 Summary of nephropathy endpoints - TS

	Patients on metformin at baseline		All patients	
	Placebo	**All empa**	**Placebo**	**All empa**
Patients in analysis set, N	1734	3459	2333	4687
New onset or worsening of nephropathy (composite)[1]				
Analysed patients, N (100%)	1552	3080	2061	4124
Patients with event, N (%)	263 (16.9)	382 (12.4)	388 (18.8)	525 (12.7)
Incidence rate per 1000 years at risk	66.5	46.1	76.0	47.8
Hazard ratio vs. placebo (95% CI)	–	0.68 (0.58, 0.79)	–	0.61 (0.53, 0.70)
New onset of macroalbuminuria (UACR >300 mg/g)[2]				
Analysed patients, N (100%)	1529	3058	2033	4091
Patients with event, N (%)	215 (14.1)	337 (11.0)	330 (16.2)	459 (11.2)
Incidence rate per 1000 years at risk	54.5	40.7	64.9	41.8
Hazard ratio vs. placebo (95% CI)	–	0.73 (0.61, 0.86)	–	0.62 (0.54, 0.72)
Doubling of serum creatinine[3] with eGFR ≤45 mL/min/1.73m^2				
Analysed patients, N (100%)	1728	3432	2323	4645
Patients with event, N (%)	50 (2.9)	50 (1.5)	60 (2.6)	70 (1.5)
Incidence rate per 1000 years at risk	10.7	5.2	9.7	5.5
Hazard ratio vs. placebo (95% CI)	–	0.49 (0.33, 0.72)	–	0.56 (0.39, 0.79)

The following component endpoints of the composite are not shown because the number of patients with events per treatment group was low: initiation of continuous renal replacement therapy (with a total of 27 events in the entire trial population); death due to renal disease (3 events in total in the entire trial population)
[1] Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.0112
[2] Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.0011
[3] Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.1556

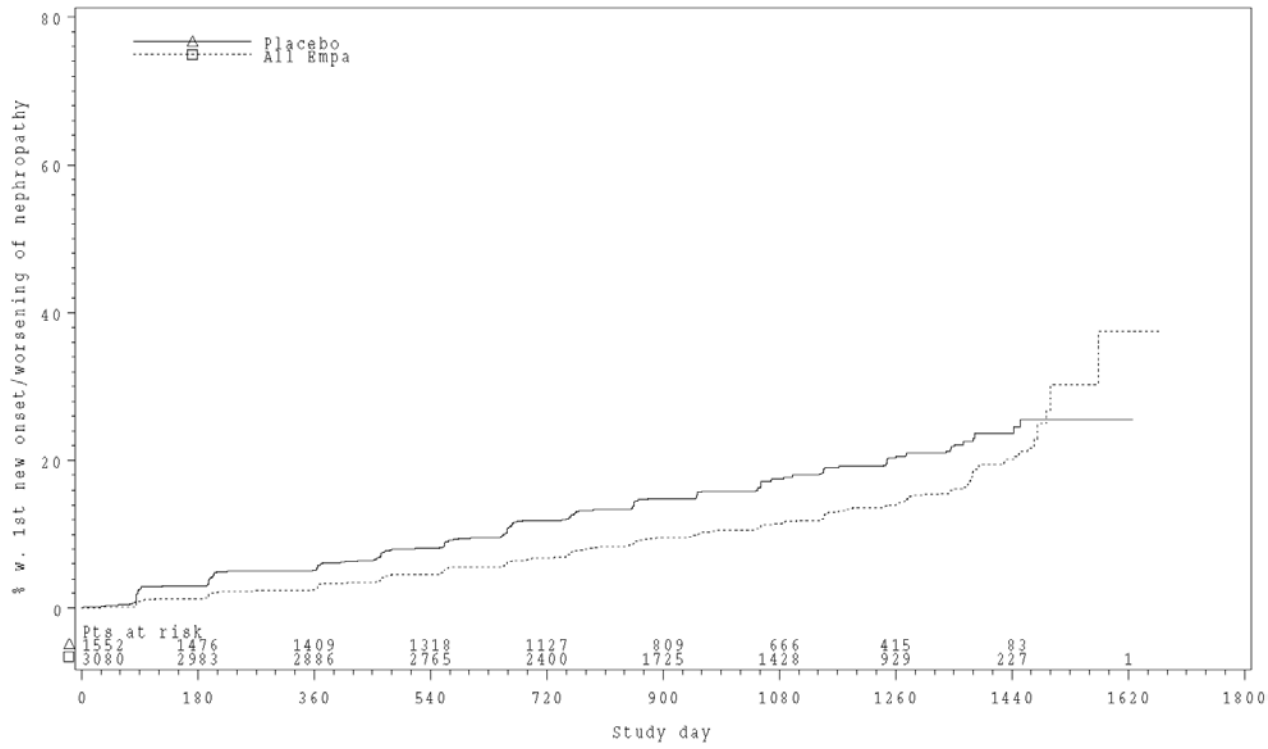

Figure 9 Kaplan-Meier estimates of time to first new or worsening nephropathy, all empagliflozin vs. placebo – TS (metformin at baseline)

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 11), no significant difference between empagliflozin and placebo was observed for new onset of albuminuria (UACR ≥30 mg/g; Table 12).

Table 12 New onset of albuminuria (UACR ≥30 mg/g) – TS

	Patients on metformin at baseline		All patients	
	Placebo	All empa	Placebo	All empa
Analysed patients, N (100%)	1068	2094	1374	2779
Patients with event, N (%)	545 (51.0)	1063 (50.8)	703 (51.2)	1430 (51.5)
Incidence rate per 1000 years at risk	260.5	245.5	266.0	252.5
Hazard ratio vs. placebo (95% CI)	–	0.95 (0.86, 1.06)	–	0.95 (0.87, 1.04)

Treatment by metformin at baseline interaction for all empagliflozin: p = 0.8440

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 (Table 13).

Table 13 Sustained reversal of macroalbuminuria– TS

	Patients on metformin at baseline		All patients	
	Placebo	**All empa**	**Placebo**	**All empa**
Analysed patients, N (100%)	178	334	257	499
Patients with event, N (%)	49 (27.5)	168 (50.3)	74 (28.8)	248 (49.7)
Incidence rate per 1000 years at risk	139.0	303.1	155.2	304.2
Hazard ratio vs. placebo (95% CI)	–	1.99 (1.44, 2.74)	–	1.82 (1.40, 2.37)

Sustained reversal required 2 consecutive measurements (at least 4 weeks apart) that fulfilled the condition.
Treatment by metformin at baseline interaction for all empagliflozin vs. placebo: p = 0.3087

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 9). 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.

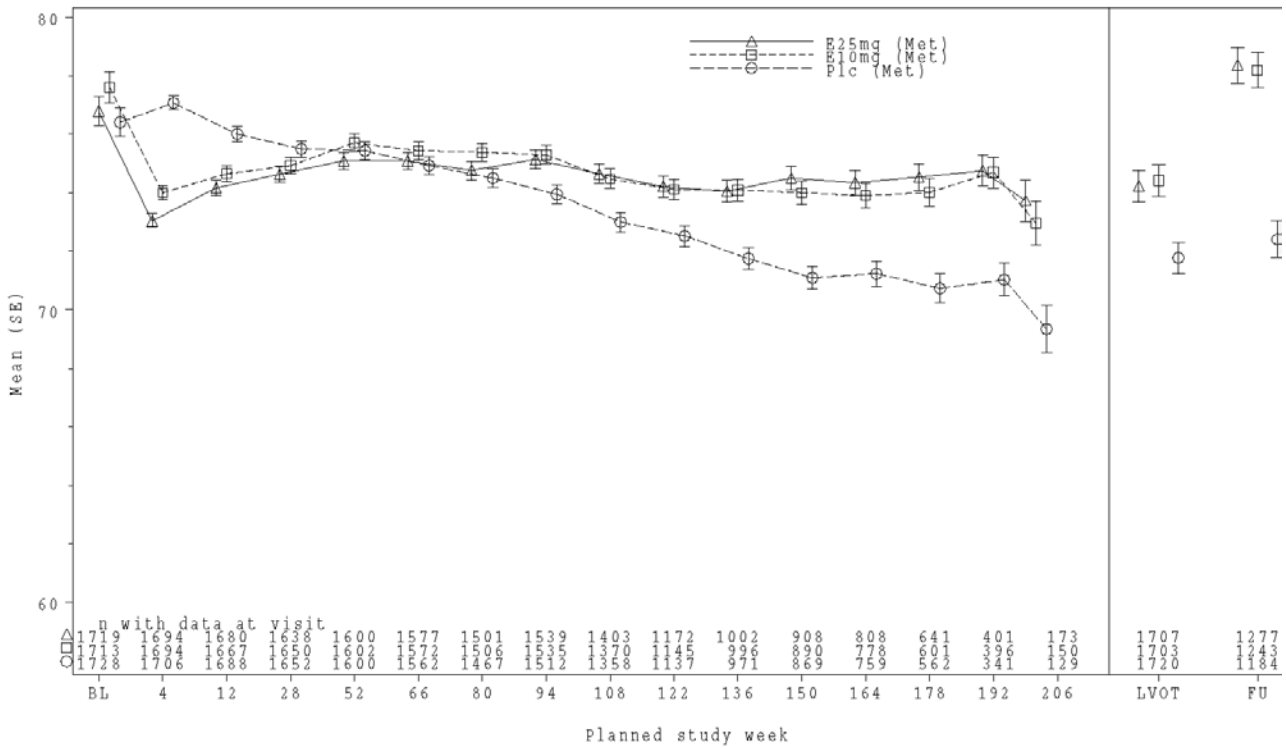

Figure 10 eGFR [mL/min/1.73m^2] MMRM results over time (OC-AD), with unadjusted last value on-treatment and follow-up value (OR, patients with available LVOT and FU values) – TS (metformin at baseline)

Further Efficacy endpoints

The protocol encouraged the investigators to treat CV risk factors such as hyperlipidemia, high blood pressure, albuminuria, unhealthy lifestyle, or smoking according to standard of care to eliminate the effect of confounding factors for the analysis of CV outcome. In a high CV risk population, this usually implies liberal addition and modification of anti-diabetic and other background therapy. In fact, anti-diabetic rescue medication was added or increased (except for the first 12 weeks) in study 1245.25 in patients receiving empagliflozin 10 mg by 33.1%, empagliflozin 25 mg by 31.8%, and placebo by 54.2% of patients.

The main focus of the CV outcome study was to monitor long-term CV safety of empagliflozin. Although the design reflects in principle the real-world effectiveness, the results are different from those gained in pivotal studies which focused on the efficacy of empagliflozin, evaluated as change from baseline in HbA1c.

The results on HbA_{1c}, FPG, body weight, SBP and DBP in this study were affected by change in background therapies such as anti-diabetic and antihypertensive medications. Therefore, the applicant believes that a direct comparison of HbA1c, blood pressure, and weight from study 1245.25 with other phase 3 studies does not have scientific merit and is potentially misleading.

Still, reductions in HbA_{1c}, FPG, body weight, SBP, and DBP were seen for empagliflozin compared with placebo. The analyses of the efficacy endpoints were only performed for the overall trial population

Table 14 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

In Figure 11, a comparison is presented between all patients and those taking metformin at baseline for the endpoints discussed above.

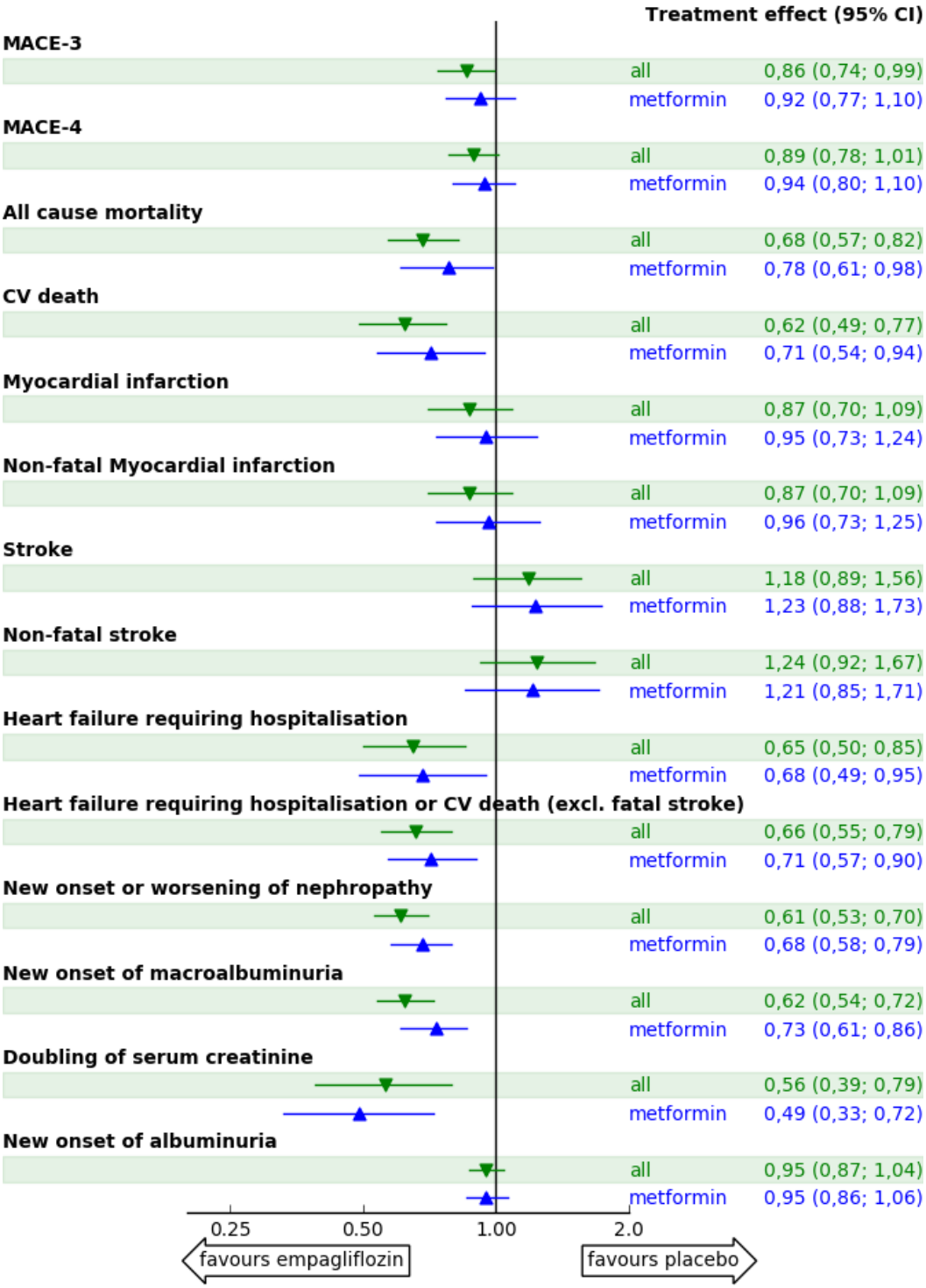

Figure 11 Comparison of endpoints in all patients and those taking metformin at baseline.

Summary of main study

The following tables summarise the efficacy results from the main studies 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 15 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 on-treatment 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 the 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

Analysis in subjects using metformin at baseline

Population		Intention to treat		
Time points		Treated set (until 30 days after treatment discontinuation		
Descriptive statistics	Treatment group		Placebo	All Empa
		Number of subjects	1734	3459
	MACE-3	N (%)	189 (10.9)	344 (9.9)
		Incidence/1000py	38.9	35.3
	MACE-4	N (%)	230 (13.3)	427 (12.3)
		Incidence/1000py	48.1	44.6
	Hosp-HF	N (%)	59 (3.4)	79 (2.3)
		Incidence/1000py	11.9	7.9
	Nephropathy	N (%)	263 (16.9)	382 (12.4)
		Incidence/1000py	66.5	46.1
	All-cause mortality	N (%)	115 (6.6)	176 (5.1)
		Incidence/1000py	22.5	17.1
	CV mortality	N (%)	84 (4.8)	118 (3.4)
		Incidence/1000py	16.4	11.5
	Non-CV mortality	N (%)	31 (1.8)	58 (1.7)
		Incidence/1000py	6.1	5.6

Effect estimate per comparison	Comparison			all empa v placebo
	Primary endpoint	MACE-3	HR	0.92
			95% CI	0.77, 1.10
	Key secondary endpoint	MACE-4	HR	0.94
			95% CI	0.80, 1.10
	Secondary endpoint	Hosp-HF	HR	0.68
			95% CI	0.49, 0.95
	Exploratory endpoint	Nephropathy	HR	0.68
			95% CI	0.58, 0.79
		All-cause mortality	HR	0.78
			95% CI	0.61, 0.98
		CV mortality	HR	0.71
			95% CI	0.54, 0.94
		Non-CV mortality	RR	0.93

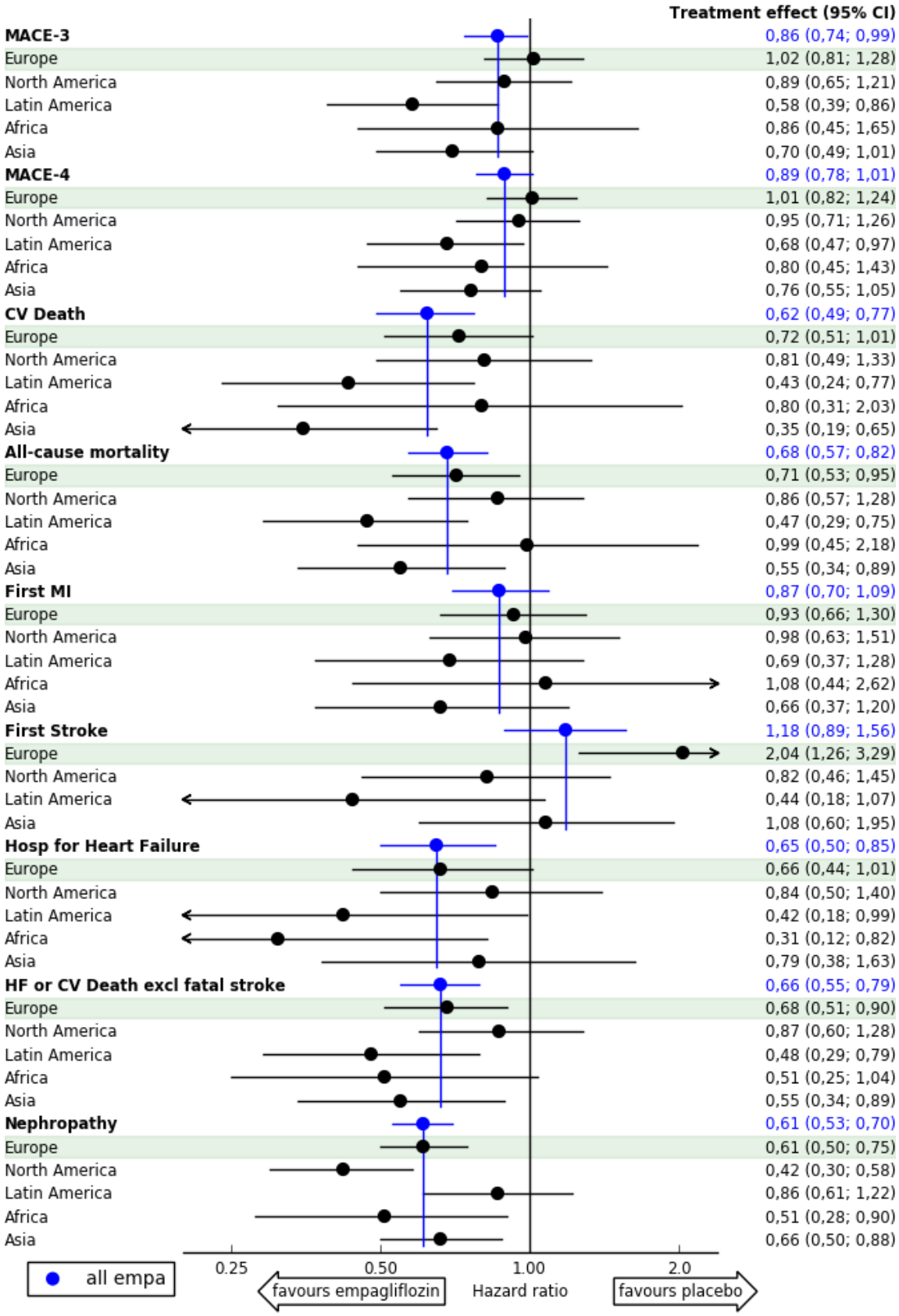

Figure 12 Subgroups by geographic region for selected endpoints (all patients, with or without metformin).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

EMPA-REG was a cardiovascular outcome trial in type 2 diabetes patients. The primary objective of such trials 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 Synjardy, 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. In these patients also metformin could be used, although it was contraindicated in Europe during the time when the trial was conducted. 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.

Empagliflozin was administered once daily, whereas in Synjardy it is administered twice daily. In the original MAA for Synjardy, differences between once or twice daily administration were assessed as not

clinically relevant. The daily metformin dose was in the range that can be achieved with Synjardy in 44.5% of metformin using patients (below 1700 mg: 34.5%, above 2000 mg: 21%). Of the randomised patients, 74.0% used metformin.

Efficacy data and additional analyses

The primary endpoint (**3-point MACE**) showed superiority of "all empagliflozin" treatment to placebo if analysed without consideration of background therapy. 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). 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 all-cause death can be translated into a number needed to treat (NNT) of 67 to prevent 1 death in 3.2 years among metformin users. This number is clearly larger than the NNT of 39 obtained in the entire trial population.

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 is 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, which 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-Meier 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 (e.g. in terms of differences in baseline parameters or background treatment) for the findings in Europe has been identified. These 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 empagliflozin 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 2 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.

When the results of subjects using metformin at baseline are compared to the overall trial population (Figure 10), a high level of consistency is obvious, but the results among metformin users are somewhat mitigated compared to all patients. The MAH emphasizes that even if the result seems less than additive, still a benefit for empagliflozin (and metformin) exists.

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. For Jardiance, 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.

Treatment with metformin was not a randomised treatment but a possible antidiabetic background medication in this study; patients who were not on metformin at baseline but started metformin only during the trial were excluded from this analysis.

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, that was driven by benefits on CV mortality and the 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 using metformin as background therapy, the benefits are maintained, but the risk reduction is mitigated.

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.

Patient exposure

The median observation period was about 3.2 years for each treatment group. The total observation time per treatment group using metformin at baseline was at least 5112 years (Table 17 **Observational period – TS**). The total exposure to treatment per group (all patients) was at least 5747 years (Table 18 Exposure to randomised trial medication – TS (all patients).

Table 16 Observational period – TS

	Patients on metformin at baseline		All patients	
	Placebo	All empa	Placebo	All empa
Treated patients, N (%)	1734	3459	2333	4687
Observation time categories, N (%)				
≥52 weeks	1700 (98.0)	3408 (98.5)	2279 (97.7)	4607 (98.3)
≥104 weeks	1514 (87.3)	3045 (88.0)	2002 (85.8)	4106 (87.6)
≥156 weeks	925 (53.3)	1847 (53.4)	1201 (51.5)	2464 (52.6)
≥208 weeks	135 (7.8)	299 (8.6)	173 (7.4)	385 (8.2)
≥260 weeks	0	0	0	3 (0.1)
Observation time [years]				
Median	3.20	3.20	3.07	3.15
Mean (SD)	2.95 (0.80)	2.97 (0.79)	2.91 (0.82)	2.96 (0.89)
Total observation time [years]	5112.4	10271.8	6794.5	13865.6

The observational period was calculated as date of last observation minus date of randomisation, plus one day.

Table 17 Exposure to randomised trial medication – TS (all patients)

	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).

Most frequently reported Adverse Events

AE incidence rates and patterns were generally consistent between the entire trial population and the patients who received metformin at baseline.

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 (metformin subgroup – empagliflozin 10 mg: 3.80/100 patient-years; 25 mg: 3.33/100 pt-yrs) than for placebo (8.24/100 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 less frequently in the placebo group for metformin users but not for all users.

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 (metformin subgroup – empagliflozin 10 mg: 7.1%; 25 mg: 7.0%) than for placebo (8.9%). The frequencies of severe events at the PT level within the SOC cardiac disorders tended to be slightly lower for the empagliflozin groups than for placebo. For infections and infestations, the most frequently reported PT, pneumonia, was reported in the entire trial population at slightly lower frequencies for patients in the empagliflozin groups than placebo; in the metformin subgroup, frequencies were similar in all 3 treatment groups. With regard to severe nervous system disorders, the frequency of ischaemic stroke was slightly lower for the empagliflozin groups (metformin subgroup – empagliflozin 10 mg: 0.3%; 25 mg: 0.1%) than for placebo (0.5%). The frequency of cerebrovascular accident was higher for the empagliflozin groups than placebo in the entire trial population and in the metformin subgroup (placebo: 26/1730, 1.5%; 60/3459, 1.7%).

Serious adverse events / 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 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 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 (metformin at baseline: placebo 27 (1.6%); empa 10 mg: 34 (2.0%); empa 25 mg 42 (2.4%)). However, the incidence rates for combined fatal or immediately-life-threatening SAEs, overall and for the SOC cardiac disorders, were lower for empagliflozin.

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 and urinary tract infections were higher in the empagliflozin 10 mg and 25 mg groups than in the placebo group.

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** (2 of these in the metformin subgroup) and the rates were comparable in all groups. The frequencies of confirmed hypoglycaemic adverse events were also comparable in all groups, including frequencies for events where the patient required assistance. The above observations were true for the entire trial population as well as for the subgroup of patients on metformin at baseline.

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

No new safety issues were identified in the analysis of laboratory results

Safety in special populations

The incidence of AEs and SAEs increases with age, but similarly in placebo and empagliflozin-treated groups. No specific data were provided for users of metformin at baseline. For the tables, reference is made to the AR of Jardiance.

Table 18 Adverse event overall summary - TS

	Patients on metformin at baseline						All patients					
	Placebo		Empa 10 mg		Empa 25 mg		Placebo		Empa 10 mg		Empa 25 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Patients	1734		1729		1730		2333		2345		2342	
Patients with any AE	1586 (91.5)	173.44	1547 (89.5)	147.29	1566 (90.5)	147.34	2139 (91.7)	178.67	2112 (90.1)	150.34	2118 (90.4)	148.36
Severe AEs[1]	410 (23.6)	NA	379 (21.9)	NA	385 (22.3)	NA	592 (25.4)	NA	536 (22.9)	NA	564 (24.1)	NA
Drug-related AEs[2]	394 (22.7)	10.63	506 (29.3)	14.42	469 (27.1)	12.99	549 (23.5)	11.33	666 (28.4)	14.15	643 (27.5)	13.38
AEs leading to discont.[3]	323 (18.6)	7.79	283 (16.4)	6.62	272 (15.7)	6.28	453 (19.4)	8.26	416 (17.7)	7.28	397 (17.0)	6.89
Serious AEs[4]	715 (41.2)	21.21	617 (35.7)	17.10	643 (37.2)	17.94	988 (42.3)	22.34	876 (37.4)	18.20	913 (39.0)	19.39
Fatal	79 (4.6)	1.80	65 (3.8)	1.45	51 (2.9)	1.12	119 (5.1)	2.06	97 (4.1)	1.61	79 (3.4)	1.31
Immediately life threatening	27 (1.6)	NA	34 (2.0)	NA	42 (2.4)	NA	44 (1.9)	0.77	53 (2.3)	0.89	60 (2.6)	1.00
Disabling	18 (1.0)	NA	12 (0.7)	NA	16 (0.9)	NA	24 (1.0)	NA	18 (0.8)	NA	22 (0.9)	NA
Requiring hospitalisation	620 (35.8)	NA	533 (30.8)	NA	576 (33.3)	NA	852 (36.5)	NA	751 (32.0)	NA	818 (34.9)	NA
Prolonging hospitalisation	51 (2.9)	NA	31 (1.8)	NA	52 (3.0)	NA	74 (3.2)	NA	52 (2.2)	NA	67 (2.9)	NA
Congenital anomaly	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA
Other	126 (7.3)	NA	99 (5.7)	NA	100 (5.8)	NA	173 (7.4)	NA	151 (6.4)	NA	147 (6.3)	NA

NA = Not analysed

[1] Worst intensity recorded

[2] As assessed by the investigator

[3] Non-serious and serious AEs

[4] A patient could be counted in more than 1 seriousness category

Table 19 Overall summary of adverse events of special interest – TS

	Patients on metformin at baseline						All patients					
	Placebo		Empa 10 mg		Empa 25 mg		Placebo		Empa 10 mg		Empa 25 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Patients	1734		1729		1730		2333		2345		2342	
Patients with AESIs												
Decreased renal function (SMQ)	122 (7.0)	2.87	79 (4.6)	1.80	82 (4.7)	1.85	155 (6.6)	2.77	121 (5.2)	2.07	125 (5.3)	2.12
Hepatic injury (SMQ)	83 (4.8)	1.94	57 (3.3)	1.29	61 (3.5)	1.37	108 (4.6)	1.91	80 (3.4)	1.35	88 (3.8)	1.48
Urinary tract infections (BIcMQ)	304 (17.5)	7.76	306 (17.7)	7.69	312 (18.0)	7.72	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
Genital infections (BIcMQ)	32 (1.8)	0.74	119 (6.9)	2.78	121 (7.0)	2.79	42 (1.8)	0.73	153 (6.5)	2.66	148 (6.3)	2.55
Confirmed hypoglycaemic AEs[1]	453 (26.1)	NA	458 (26.5)	NA	473 (27.3)	NA	650 (27.9)	NA	656 (28.0)	NA	647 (27.6)	NA
Bone fracture (BIcMQ)	66 (3.8)	1.53	63 (3.6)	1.44	53 (3.1)	1.18	91 (3.9)	1.61	92 (3.9)	1.57	87 (3.7)	1.46
Volume depletion (BIcMQ)	78 (4.5)	1.82	78 (4.5)	1.79	82 (4.7)	1.85	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
Malignancies (BIcMQ)	58 (3.3)	1.33	69 (4.0)	1.56	70 (4.0)	1.56	78 (3.3)	1.36	106 (4.5)	1.79	96 (4.1)	1.61
Malign. up to trial termination	70 (4.0)	1.42	76 (4.4)	1.55	79 (4.6)	1.59	103 (4.4)	1.57	117 (5.0)	1.76	110 (4.7)	1.65
Hypersensitivity (SMQ)	151 (8.7)	3.62	118 (6.8)	2.75	134 (7.7)	3.09	197 (8.4)	3.59	158 (6.7)	2.75	181 (7.7)	3.14
Venous emb./thromb. AEs (SMQ)	14 (0.8)	0.32	6 (0.3)	0.13	14 (0.8)	0.31	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35
Diabetic ketoacidosis (BIcMQ)	0	0	1 (0.1)	0.02	1 (0.1)	0.02	1 (<0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02

BIcMQ = BI customised MedDRA query; NA = not analysed; SMQ = standardised MedDRA query
A patient could be counted in more than 1 category.
[1] Any hypoglycaemic AE with a plasma glucose concentration ≤70 mg/dL or requiring assistance

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. The overall incidence rate of (complicated) UTIs was higher in the empagliflozin groups and the placebo group among users of metformin at baseline (but not in the entire trial). 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 (all subjects: 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 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:

The PRAC considered that the risk management plan version **8.4** 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 **8.4** with the following content:

Safety concerns

Summary of the safety concerns

Important identified risks	Urinary tract infection
	Genital infection
	Volume depletion
	Hypoglycaemia (with insulin and/or SU)
	Lactic acidosis
	Diabetic ketoacidosis with atypical presentation
Important potential risks	Urinary tract carcinogenicity
	Liver injury
	Bone fracture
Missing information	Paediatric patients
	Elderly patients (≥85 years)
	Pregnancy/breast-feeding

Pharmacovigilance plan

Study / activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
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 patients treated with empagliflozin compared with users of other antidiabetic treatment.	Urinary tract infection, genital infection, acute renal failure, liver injury, and 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 patients treated with empagliflozin compared with users of other antidiabetic treatment.	Urinary tract carcinogenicity	Started	Final report June 2021
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

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

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, 4.8, and 4.9. Prescription-only medicine.	None
Lactic acidosis	Labelling in SmPC sections 4.2, 4.4, 4.8, and 4.9. 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, 4.3, 4.4, and 4.8. 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, 4.4, and 4.8. Prescription-only medicine.	None
Pregnancy/breast-feeding	Labelling in SmPC section 4.6. 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, 4.2 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, sections 4.4, 4.8 of the SmPC have been updated with additional safety information pertaining to elevated haematocrit, volume depletion, thirst, serum lipids increased. Minor editorial changes have also been introduced.

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

3. Benefit-Risk Balance

Synjardy 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 . During the assessment, also modification of the current indication was discussed. A similar variation for Jardiance was recently agreed by CHMP.

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). At baseline, 74% of the participants used metformin. The patients 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. The results were similar in the subgroup of users taking metformin at baseline. In this subgroup, patients with events were 189/1734 (10.9%) for placebo and 344/3459 (9.9%) for all empagliflozin treated patients. The HR was 0.92 (95% CI: 0.77, 1.10). The results were similar (although not statistically significant) in exploratory analyses for both empagliflozin doses

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 the lower frequency of CV death (placebo: 84 (4.8%), all empa: 118 (3.4%)). The most prevalent categorisations of the CV deaths were “other CV death”, including fatal events deemed not assessable by the CEC (in all patients: 129 of 309 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:0.96; 95% CI 0.73, 1.25). Although not statistically significant, the hazard ratio point estimate for **stroke** was above 1 (non-fatal stroke; HR 1.21; 95% CI 0.85, 1.71). In Europe, the HR for stroke was statistically significant (all patients: HR 2.04, CI: 1.26, 3.29). The adverse effect on strokes was similar independent of metformin background use.

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 0.94 (95% CI 0.80, 1.10)). 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 among metformin users: placebo: 115 (6.6%), empa: 176 (5.1%)). 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 slightly reduced in the empagliflozin group compared with the placebo group. The result was confirmed in a sensitivity analysis for all patients 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.

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 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 3.4%, All empa 2.3%; HR: 0.68 (CI: 0.49, 0.95)).

The exploratory composite **nephropathy** endpoint "new or worsening nephropathy" was reduced for empagliflozin (HR 0.68 (95% CI: 0.58, 0.79). 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.

In all patients, there were slight advantages for the higher dose in parameters like HbA1c, FPG, blood pressure and weight, but these results (and their comparison to placebo) were not reported for metformin users. Similarly, the results in subjects with or without insulin at baseline should be provided for assessment.

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 in Europe in all patients (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.

When the results of subjects using metformin at baseline are compared to the overall trial population, a high level of consistency is obvious, but the results among metformin users are mitigated compared to all patients (Figure 10).

Risks

Unfavourable effects

The safety profile of empagliflozin in the EMPA-REG trial (1245.25) was consistent with the known safety profile of empagliflozin. 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 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 ketoacidosis (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.

In metformin users, the AE pattern was consistent with the overall trial population.

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 20 Effects Table for cardiovascular risk prevention by empagliflozin in users of metformin at baseline

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	9.9	10.9	Primary endpoint All patients: HR* 0.86 (0.74, 0.99) P (2-sided) = 0.0382 Metformin at baseline: HR* 0.92 (0.77, 1.10) Uncertainties: Fatal/non-fatal MI: HR* 0.95 (0.73, 1.24) Fatal/non-fatal Stroke: HR* 1.23 (0.88, 1.73). In European subgroup (all patients), HR 2.04, (1.26, 3.29).
CV Death	Mortality Adjudicated to CV cause	% of patients with event	3.4 ***	4.8	Exploratory analysis of component of primary endpoint. HR* 0.71 (0.54, 0.94)
Hospitalisation for heart failure	Adjudicated events of hospitalisation for heart failure	% of patients with event	2.3	3.4	Exploratory analysis HR* 0.68 (0.49, 0.95)
New or worsening nephropathy	any of New onset of macro-albuminuria (UACR >300 mg/g), doubling of serum creatinine level accompanied by an eGFR ≤45**, initiation of continuous renal replacement therapy or death due to renal disease	% of patients with event	12.4	16.9	Exploratory analysis HR* 0.68 (0.58, 0.79)
Unfavourable Effects					
Any AE	Rate of patients reporting any AE.	Incidence per 100 patient yrs	10 mg: 147.29 25 mg: 147.34	173.44	As assessed in EMPA-REG, result consistent with phase 3 program
Hypoglycaemia	Rate of patients reporting the AE (company query).	Incidence per 100 patient yrs	10 mg: 14.20 25 mg: 14.18	13.86	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 yrs	10 mg: 7.69 25 mg: 7.72	7.76	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 yrs	10 mg: 2.78 25 mg: 2.79	0.74	As assessed in EMPA-REG, result consistent with phase 3 program
Ketoacidosis	Number of patients reporting the AE.		10 mg: 1 25 mg: 1	0	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 is 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. Among metformin users, the NNT is 67 to prevent 1 death in 3.2 years. 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 with eGFR between 30 and 60 ml/min/1.73m^2, who could not use Synjardy. Since finalisation of the metformin Article 31 referral (EC decision 13 December 2016), use of Synjardy in these patients can be expanded. 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 when eGFR is below 45 ml/min 1.73 m^2.

The safety profile confirms prior knowledge, no unexpected adverse effects occurred. As usual for this class of products, urogenital infections were more frequent among empagliflozin users. Bone fractures were not more frequent in empagliflozin treated patients. Ketoacidosis occurred in only 2 cases (both on empagliflozin) among patients using metformin. Malignancies occurred slightly more frequently in the

empagliflozin-treated groups, but no specific malignancy was noticeable as 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 or baseline differences. 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

This Type II variation for Synjardy runs in parallel with a similar variation for Jardiance (empagliflozin, EMEA/H/C/002677/II/0014) which was finalised by CHMP in December 2016. The conclusion of that procedure will be the basis of the decision for Synjardy. The currently proposed revised indication statement is aligned with Jardiance.

As more than 70% of the subjects in EMPA-REG were also metformin users (who are the focus of this document), similar results to the entire trial population are expected. Indeed, no important differences between the entire trial population and the subgroup of metformin users are found, although the benefits among metformin users are somewhat mitigated (Figure 10), e.g. NNT 67 to prevent 1 death in 3.2 years (metformin users) compared to 39 to prevent 1 death in 3.1 years (all patients). 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 the CHMP assessment for Jardiance 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 m^2 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 was different, as the 25 mg dose has no advantages for CV prevention compared to the 10 mg dose. 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, as part of the parallel Jardiance procedure for EMPA-REG, 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 Synjardy 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.

In line with the previous CHMP opinions on Jardiance and Jentadueto, the following indication was agreed by the CHMP:

"Synjardy is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the population studied, see sections 4.4, 4.5 and 5.1."

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

Modification of the indication for Synjardy to reflect new data on cardiovascular outcomes based on study 1245.25 (EMPA-REG OUTCOME). As a consequence the SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 have been updated. The Package Leaflet and RMP have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes.

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