22 June 2023
EMA/304328/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Jardiance

International non-proprietary name: empagliflozin

Procedure No. EMEA/H/C/002677/II/0074

Marketing authorisation holder (MAH) Boehringer Ingelheim International GmbH

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List of abbreviations

3P-MACE : 3-point major adverse cardiovascular event

ACEi : Angiotensin-converting enzyme inhibitor

AE : Adverse event

AESI : Adverse event of special interest

ARB : Angiotensin receptor blocker

BI : Boehringer Ingelheim

BIcMQ : Boehringer Ingelheim customized MedDRA Query

CI : Confidence interval

CKD : Chronic kidney disease

CTR : Clinical trial report

CV : Cardiovascular

DMC : Data Monitoring Committee

eGFR : Estimated glomerular filtration rate

ESKD : End-stage kidney disease

GCP : Good clinical practice

HHF : Hospitalisation for heart failure

HR : Hazard ratio

ICH : International conference on harmonisation

MedDRA : Medical dictionary for regulatory activities

MMRM : Mixed model with repeated measurements

NT-proBNP : N-terminal prohormone of brain natriuretic peptide

OC-AD : Observed Case-All Data

OC-OT : Observed Case-On Treatment

PEC : Predicted Environmental Concentration

PT : Preferred term

PBRER : Periodic benefit-risk evaluation report

RAAS : Renin-angiotensin system inhibitors

RAS inhibitors : Renin-angiotensin system inhibitors

RS : Randomised Set

SAE : Serious adverse event

SD : Standard deviation

SGLT : Sodium-glucose co-transporter

SMQ : Standardized MedDRA Queries

SOC : System organ class

TS : Treated Set

UACR : Urine albumin to creatinine ratio

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 21 November 2022 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 of chronic kidney disease (CKD) in adults, based on final results from study EMPA-KIDNEY (1245-0137) listed as a category 3 study in the RMP; this is a Phase III, multicentre international randomised parallel group double-blind placebo controlled clinical trial of empagliflozin once daily to assess cardio-renal outcomes in patients with chronic kidney disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 19.0 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

The variation requested 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/0082/2019 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 MAH 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 MAH received Scientific Advice from the CHMP on 9 November 2017 (EMA/CHMP/SAWP/715563/2017).

The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	21 November 2022
Start of procedure	31 December 2022
CHMP Rapporteur Assessment Report	2 March 2023
PRAC Rapporteur Assessment Report	3 March 2023
PRAC members comments	8 March 2023
CHMP Co-Rapporteur Assessment	8 March 2023
Updated PRAC Rapporteur Assessment Report	17 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	30 May 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	15 June 2023
Opinion	22 June 2023

2. Scientific discussion

2.1. Introduction

This application is based upon the single pivotal trial EMPA-KIDNEY (1245.137), which was designed to support a new indication for the use of Jardiance (empagliflozin) 10 mg for the treatment of CKD: *Jardiance is indicated in adults for the treatment of chronic kidney disease.*

2.1.1. Problem statement

Disease or condition

Chronic kidney disease is increasingly recognized as a global public health problem affecting 10-15% of the population worldwide. Chronic kidney disease results from a variety of causes, such as diabetes, hypertension, vascular disease, or glomerulonephritis, but diabetes remains the leading cause of this condition. Approximately 40% of patients with type 2 diabetes have CKD based on eGFR or albuminuria criteria, and over 20% have clinically overt CKD (eGFR below 60 mL/min/1.73m2).

Chronic kidney disease is associated with excess risk for cardiovascular disease (CVD). Indeed, CV risk, including heart failure episodes and mortality, increases as eGFR decreases below 60 mL/min/1.73m2, independent of other risk factors, including diabetes. Cardiovascular events are the most frequent cause of death in patients with CKD. In addition, high levels of albuminuria (Urine Albumin-to-Creatinine Ratio; UACR ≥30 mg/g), are associated with an increased risk of all-cause and cardiovascular mortality.

CKD is associated with impaired quality of life and substantially reduced life expectancy at all ages. End-stage renal failure (ESRD) is the most severe form of CKD and is fatal if not treated by renal replacement therapy. Although patients with early CKD are more likely to die before they reach ESRD, the avoidance of ESRD is still highly desirable due to its adverse effects on quality of life and the substantial costs of dialysis and transplantation to healthcare providers. Although Renin-Angiotensin System (RAS) blockade with Angiotensin-converting enzyme inhibitor (ACEi) or Angiotensin receptor blockers (ARB) have been shown to reduce albuminuria and slow the rate of progression in proteinuric nephropathies, particularly in diabetic kidney disease, a substantial residual risk of ESRD remains. In summary, there is a high unmet medical need for new treatment options that can be added safely to current standard treatments in CKD, with a primary aim to slow the progression of CKD and reduce the risk of CV death.

2.1.2. About the product

Jardiance (empagliflozin) is a selective sodium-glucose co-transporter-2 (SGLT-2) inhibitor, and empagliflozin causes urinary glucose excretion and reduces hyperglycaemia, weight, plasma circulating volume and blood pressure. This has been shown to translate safely into reduced clinical risk from cardiovascular disease (particularly heart failure and cardiovascular death) in people with type 2 diabetes (T2D) and established cardiovascular disease. SGLT-2 inhibition with empagliflozin also reduces albuminuria and slows the annual decline in estimated glomerular filtration rate in people with T2D who still have preserved kidney function. The kidney effects may result from increased sodium delivery to the kidney's macula densa, which in turn causes glomerular afferent arteriolar vasoconstriction and reduced intraglomerular pressure. Raised intraglomerular pressure is believed to be central to the "final common pathway" of disease progression in chronic kidney disease (CKD). Since SGLT-2 inhibition with empagliflozin also causes glycosuria and acute haemodynamic changes in kidney function in people without diabetes, empagliflozin may also be nephroprotective in conditions without ambient hyperglycaemia, which collectively accounts for 50 to 70% of patients with CKD worldwide. Patients with established CKD are at substantial risk of progressing to end-stage kidney disease despite the use of medical therapies, including renin-angiotensin system inhibition, so identifying new treatments to delay progression is a priority.

Empagliflozin was developed by Boehringer Ingelheim (BI), and is approved and marketed for the treatment of type 2 diabetes mellitus (T2DM), prevention of cardiovascular (CV) events in adults with T2DM and established CV disease, and for the treatment of adults with heart failure independent of left ventricular ejection fraction.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Scientific advice from the CHMP/SAWP on 9 November 2017 (EMA/CHMP/SAWP/715563/2017). The Scientific advice pertained to clinical aspects of the dossier with some important points as mentioned below:

- The Applicant is advised to follow the Guideline on the clinical investigation of medicinal products to prevent the development/slow progression of chronic renal insufficiency: EMA/CHMP/500825/2016

- A separate indication based on this target population could be acceptable, depending on the final study results, in particular, providing that a beneficial treatment effect is not predominately a consequence of improving glycaemic control in the part of the trial population with Diabetes Mellitus.
- Inclusion of patients with (a) eGFR ≥20 <45 mL/min/1.73^2; or (b)eGFR ≥45 mL/min/1.73m2 with urinary albumin/creatinine ratio ≥200 mg/g (or protein/creatinine ratio≥300 mg/g), is generally acceptable. Patients with polycystic nephropathy and those receiving immunosuppressive medication are excluded; thus, the trial is not fully representative of the whole CKD population. Immunosuppression with a potency greater than prednisolone 10 mg or immunosuppression with non-corticosteroids in the last 3 months is expected to be small. Still, this patient population will be excluded as it represents a vulnerable patient population, and patient safety is of utmost importance. The CHMP acknowledged the explanation and confirmed the proposed approach.
- The trial should be designed to demonstrate beneficial effects across the range of aetiologies and stages.
- The selected dose of 10 mg empagliflozin is agreed.
- The trial had been specifically designed to ensure that clear evidence of the effects of empagliflozin on renal disease progression would emerge before any beneficial effects on vascular mortality become highly significant. This would seem critical to trial interpretation to extend the indication statement in the manner proposed. On that basis, the proposed composite endpoint of the first occurrence of either of the components related to renal disease progression (i.e. end-stage renal disease [ESRD] or a sustained decline in eGFR of ≥40%), or cardiovascular (CV) death, can be accepted. However, whilst a wish to understand the effect on the underlying renal and vascular disease process is understood, other deaths cannot be ignored when interpreting the magnitude of benefit and assessing the benefit-risk. A secondary analysis, including renal disease progression events and all-cause mortality will be required. In addition, supplementary analyses treating any non-renal death, including CV death, as a competing risk should be prospectively planned. This analysis will necessarily invoke strong assumptions that should be clearly stated and explored in sensitivity analyses. In any case all-cause mortality should be analysed as a secondary outcome. Change in eGFR should be sustained; this is not guaranteed in those patients where a ≥40% decline in eGFR is observed only during the last study visit.
- The Applicant proposed the analysis of all-cause hospitalization in Section 5 of the PI and stated that hospitalization for heart failure would be adjudicated, but the analysis of all-cause hospitalization will be based on investigator reports which will not be adjudicated. This is not the preferred approach. Hospitalization reflects the disease burden for the patient and it is important to the understanding of any effect of treatment on hospitalization events to understand the cause and the extent to which hospitalisations are influenced by non-clinical considerations. Specifically, it is important to differentiate if the cause of hospitalization is related to renal disease progression and or cardiovascular disease, consistent with the primary objective of the study, from those due to other co-morbidities. Therefore, all hospitalization events would ideally be adjudicated and their definition and criteria used for evaluation should be standardized and included in the protocol. It would be harder to understand the relevance of an effect on hospitalizations based on unadjudicated data, and this might preclude their usefulness for the prescriber and hence their inclusion in the SmPC.
- In this study, the Applicant will use minimization allocation in order to maintain a 1:1 (empagliflozin vs placebo) ratio within strata (instead of the typically used method: blocked randomization) with no consideration of re-randomizations methods for analysis. The use of minimisation has possible implications on the analysis with regards to bias and Type I error control. Re-randomization tests are an appropriate approach for assessing statistical significance when a minimization algorithm is

used (cf EMA Guideline on adjustment for baseline covariates in clinical trials, 26 February 2015 EMA/CHMP/295050/2013 and Proschan et al, 2011). Re-randomization tests for the primary and secondary efficacy analysis should be considered with the use of classical tests as supportive analyses. A particular concern might be raised in the use of a Cox proportional hazards model when the trial has so many strata over which the proportional hazards assumption should hold.

- The use Hochberg procedure for testing key secondary endpoints is acceptable.
- Monitoring of severe side effects and risk for amputation in particular, is extremely important in all patients with CKD.

2.1.4. General comments on compliance with GCP

No GCP inspection was performed for the EMPA-KIDNEY trial. The EMPA-KIDNEY trial was performed in accordance with the ICH GCP, as claimed by the Applicant.

2.2. Non-clinical aspects

2.2.1. Pharmacology

Primary pharmacodynamic studies

The effects of empagliflozin on different aspects of the pathophysiology of chronic kidney diseases were studied in various pharmacological studies *in vitro* and *in vivo*. Cellular assays were done in human proximal tubular cells, and *in vivo* studies were performed in mice and rats. Importantly, studies were done in normoglycemic animals as well as animals with pre-existing diabetes in order to reproduce aspects of the beneficial results of the clinical studies and to better understand the mode of action of empagliflozin on the renal system.

Empagliflozin is a potent and selective inhibitor of the human sodium glucose cotransporter-2 (SGLT 2). By inhibition of SGLT 2 in the proximal tubules of the kidneys empagliflozin reduces the reabsorption of glucose leading to increased urinary glucose excretion and, in consequence, to a lowering of blood glucose under hyperglycemic as well as normoglycemic conditions. SGLT2 activity results in glucose / sodium absorption in a ratio of 1:1. Increased reabsorption of sodium contributes to diabetic glomerular hyperfiltration by lowering the Na-Cl-K concentrations at the macula densa and increasing glomerular filtration rate (GFR) through the physiology of tubuloglomerular feedback.

Empagliflozin normalized GFR in various animal models. The compound prevented glomerular hyperfiltration in models of DKD *in vivo*. Different CKD models with reduced GFR empagliflozin prevented glomerular damage in various species, as shown by the prevention of albuminuria. Empagliflozin also reduces sodium reabsorption, thereby increasing sodium delivery to the distal tubule.

Empagliflozin prevented inflammatory processes in diabetic as well as non-diabetic animals with kidney diseases induced by different stimuli, exhibiting both glomerular and tubulointerstitial protective measures. These effects may contribute to the beneficial effects of empagliflozin on CKD observed in humans.

Empagliflozin prevented fibrotic processes like epithelial-to-mesenchymal transition *in vitro*. Furthermore, renal remodelling, including matrix and collagen deposition, was inhibited in animals with and without diabetes mellitus.

Empagliflozin prevented the increase of reactive oxygen species *in vitro* and has been shown to inhibit or prevent oxidative stress in various pharmacological models.

Activation of the sympathetic nervous system was shown to be of pathophysiological relevance in animal models. This has been demonstrated in an Akita mouse model of diabetes mellitus as well as in a model of cyclosporine-induced kidney damage. Empagliflozin prevented activation markers of the sympathetic nervous system in both *in vivo* models.

Beneficial effects of empagliflozin on kidney disease were demonstrated in mice that showed an increase in blood levels of the ketone body beta hydroxybutyrate (b-OHB). Similar beneficial effects were obtained by experimental administration of ketone bodies to the mice.

A mild increase in plasma ketone bodies was observed with empagliflozin in clinical trials as well as in preclinical studies. Ketone bodies are discussed as additional or alternative "fuel" to glucose oxidation for the energy supply of various organs. Indeed, oxidation of ketone bodies, e.g. ß-hydroxybutyrate, appears to be an effective way to generate ATP with less oxygen consumption than glucose oxidation. Thus, ketone bodies can be regarded as an additional energy source for organs in need.

All above-mentioned effects of empagliflozin can be expected to be beneficial for the patients and may contribute to the overall nephroprotective effects in patients. The exact mechanism of empagliflozin and pathways involved in the benefits seen on the renal system, in particular on chronic kidney disease, is presently under investigation in ongoing preclinical and clinical studies.

In summary:

Human CKD is a disorder characterized by unphysiological GFR values: hyperfiltration in early DKD, loss of GFR in chronic kidney disease. In addition, inflammation, fibrotic processes and oxidative stress commonly occur in CKD. Empagliflozin improved renal function and prevented pathophysiological remodelling of the kidneys in animal models of chronic kidney disease induced by different interventions. Additionally, inflammation and oxidative stress was reduced by empagliflozin and sympathetic activation was attenuated. Further, empagliflozin might have metabolic effects providing ketone bodies as additional / alternative energy source for the diseased kidney Thus, empagliflozin showed significant beneficial effects on chronic kidney disease in a number of different pre-clinical studies in mice and rats. These effects were observed consistently in animals with T2DM as well as in non-diabetic animals.

The beneficial renal effects of empagliflozin may be directly related to SGLT2 inhibition in the kidneys. This results in the activation of a tubuloglomerular feedback mechanism, RAAS inhibition, decreased sympathetic nerve activity and increased hematocrit. In addition, metabolic effects on renal energy supply, local anti-inflammatory, anti-remodelling and anti-oxidative effects of empagliflozin may contribute to the beneficial effects of empagliflozin in patients with chronic kidney disease. However, despite the number of *in vitro* and *in vivo* experiments described here and elsewhere, the exact molecular mechanisms of empagliflozin's beneficial renal effects are still under investigation.

Secondary pharmacodynamic studies

No new secondary pharmacology studies are available.

Safety pharmacology programme

No new safety pharmacology studies are available.

Pharmacodynamic drug interactions

No new pharmacodynamic drug interaction studies are available.

2.2.2. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) for empagliflozin was submitted with the initial MAA and an updated ERA after completion of an additional study. The risk assessment resulted in the conclusion that no significant impact on the environment is expected.

In the current ERA, the estimation of the predicted environmental concentration (PEC) of empagliflozin in the various environmental compartments is based on the default market penetration factor (Fpen = 0.01), as provided in the EMA guideline, and the highest maximum daily dose of 25 mg. The recommended maximum daily dose of the newly proposed indication (Chronic Kidney Disease) will only be 10 mg.

The default Fpen is based on a very conservative worst-case estimation, meaning that 1% of all EU inhabitants are treated 365 d/a with the recommended maximum daily dose. The market penetration factor was not refined though, e.g., by using the much smaller actual amount of substance placed on the market.

Therefore, the effects on the environment by adding the new intended Chronic Kidney Disease indication with a much smaller patient group are considered negligible and well covered by the used Fpen.

The ERA tables, including calculations for all proposed indications for Jardiance, were updated as follows:

Table 1. Maximum daily doses of empagliflozin for all proposed indications for Jardiance

Treatment	Maximum daily dose
Type 2 Diabetes (approved)	25 mg
Heart Failure, reduced ejection fraction (approved)	10 mg
Heart Failure, preserved ejection fraction (approved)	10 mg
Chronic Kidney Disease (new)	10 mg

To calculate the PEC values, taking into consideration all proposed indications of Jardiance, the default market penetration factor (Fpen) of 0.01 (not refined) and the sum of the maximum daily doses, i.e. 55 mg (see Table 1), have been applied.

For the calculation of the PEC/PNEC ratios in the various environmental compartments the PNEC values as mentioned in the original Environmental Risk Assessment have been used (see Table 2 and Table 3).

Table 2. PEC and PNEC values for empagliflozin

Compartment	$PEC_{Type\ 2\ Diabetes}$ [µg/L]	$PEC_{all\ indications}$ [µg/L]	PNEC [µg/L]
Surface water	0.125	0.275	240
Microorganisms	0.125[1]	0.275[1]	≥10000
Groundwater	0.03125[2]	0.0687[2]	≥10000

[1] $PEC_{microorganisms} = PEC_{surface\ water}$

[2] $PEC_{groundwater} = 0.25 \cdot PEC_{surface\ water}$

Table 3. PEC/PNEC ratios for empagliflozin

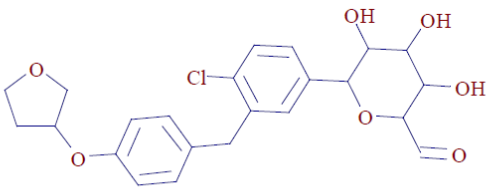
Compartment	PEC/PNEC ratio Type 2 Diabetes	PEC/PNEC ratio all indications	Trigger for Tier B
Surface water	0.00052	0.00114	1
Microorganisms	≤ 0.0000125	≤ 0.0000225	0.1
Groundwater	≤ 0.000003125	≤ 0.00000687	1

Phase II – Tier A OECD 308 and Tier B OECD 218 studies:

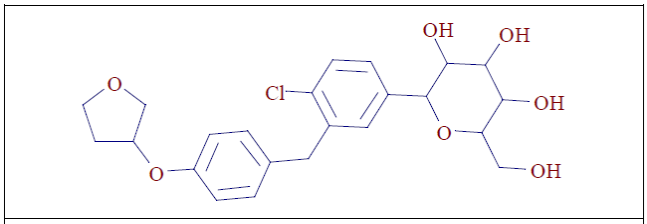
In the water sediment study, the relevant transformation products M3 and M12 generated in the water/sediment study exceeded the P trigger for sediment (M3) and water (M12), but only after conversion to 12°C EU outdoor temperature, and none of the detected transformation products showed continuously increasing concentration during the study.

Consequently, following the 'total residue approach' (EMA/CHMP/SWP/44609/2010 of 17 March 2011) a toxicity study in sediment-dwelling Chironomid larvae (OECD 218) was conducted resulting in the conclusion that the use of empagliflozin and its transformation products can be considered as insignificant environmental risk for the compartment sediment.

However, since the study on identification of metabolites indicates that metabolite M3 may be a stereoisomer of the parent compound, it might be that M3 has certain pharmacologically activity. Therefore, below, information on the structure of M3 and M1 (M12 was instable and could not be further analyzed) as well as the DT50-values for total system, sediment and water recalculated to 12 °C for empagliflozin and the relevant transformation products M3, M1 and M12 are given. M3 is very persistent in the sediment (DT50 > 180 days) and M12 is persistent in water (DT50 > 40 days).



Proposal for M1 of BI 10773: C23H25ClO7, MM 448.1289 Da



Proposal for M3 of BI 10773: C23H27ClO7, MM 450.1445 Da (Isomer of BI 10773)

Table 4. DT50-Values recalculated to 12 °C (Arrhenius equation) for empagliflozin and the relevant transformation products M1, M3 and M12

[^{14}C]BI 10773		Water		Sediment		Total System	
		River	Pond	River	Pond	River	Pond
Parent	DT_{50} (days)	2.5	2.3	5.5	4.1	2.8	2.8
M1	DT_{50} (days)	9.6	13.0	39.3	26.0	13.2	16.9
M3	DT_{50} (days)	27.3	4.7	189.8	140.9	110.4	78.5
M12	DT_{50} (days)	--	79.8	--	88.8	--	80.0

Updated ERA summary table:

The ERA summary table which is included in the original authorization of Jardiance (Table 1 in Section 2.3.4 of the EPAR) has been updated accordingly (see Table 5 below).

Table 5. Summary of the main study results

Substance (INN/Invented Name): Empagliflozin					
CAS-number (if available): 864070-44-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} = 1.73			Not potentially PBT, nor vPvB
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log K_{ow} = 1.73			not B
Persistence	DT50 or ready biodegradability	**Parent:** $DT_{50,\ 12°C\ water}$: 2.6/ 2.3 d $DT_{50,\ 12°C\ sediment}$: 5.5/4.1d Transformation products: **TP M3** (stereoisomer of empagliflozin) $DT_{50,\ 12°C\ sediment}$ **=189.8/140.9 d TP M12:** $DT_{50,\ 12°C\ water}$ **=79.8 d TP M3: very persistent** in sediment, **TP M12: very persistent** in water			**vP** (for transformation products M3 in sediment, TP M12 in water)
Toxicity	NOEC or CMR	2.4 mg/L			not T
PBT-statement	The compound is considered not PBT and not vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$ (all indications), default or refined (e.g. prevalence, literature)	0.275	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 51.5 L/kg			Mean of 49 and 54 L/kg for WWTP sludge.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 1.2/1.1 d (r/p) $DT_{50,\ sediment}$ = 2.6/1.9 d (r/p) $DT_{50,\ whole\ system}$ = 1.3/1.3 d (r/p) shifting to sediment = 26.4/25.0% (r/p)			r = river, p = pond, Significant shifting to sediment observed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcaptitat*	OECD 201	NOEC	≥ 100	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 100	mg/L	
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	NOEC	2.4	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 100	mg/L	
Phase IIb studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	1010	mg/kg	normalized to 10% Corg

Conclusion:

For all three compartments, the PEC/PNEC ratios for all proposed indications of Jardiance are clearly below the trigger values of 1 and 0.1, respectively.

Additionally, empagliflozin and its transformation products can be considered as insignificant environmental risk for the compartment sediment.

Hence, the ERA submitted with the initial MAA remains valid for the current type II variation covering the additional proposed indication.

2.2.3. Discussion on non-clinical aspects

Additional information has been provided on the pharmacologic effects in chronic kidney diseases. Although several factors have been mentioned that may contribute to the positive actions of empagliflozin on chronic kidney disease, the precise molecular mechanisms of these effects are not clear. Several possible mechanisms may play a role. SGLT2i reduces glomerular hyperfiltration via various mechanisms. Empagliflozin improved renal function and prevented pathophysiological remodelling of the kidneys in animal models of chronic kidney disease induced by different interventions. These effects were observed in animals with T2DM as well as in non-diabetic animals. Furthermore, the empagliflozin-induced increase in ketone bodies may play a role by increasing the uptake and oxidization of β-hydroxybutyrate resulting in an improved energy supply. The increase in plasma ketone bodies induced by SGLT2 inhibitors is generally mild and usually does not exceed the physiological range. Empagliflozin was also shown to reduce remodelling processes, including fibrosis *in vivo*. Further, it reduced inflammation and oxidative *stress in vivo* and *in vitro*. It is currently not clear which of the numerous potential mechanisms of action are of clinical relevance or which one would be the dominant one. The proposed mechanisms have been substantiated by the literature data and are considered acceptable.

It is agreed with the MAH that the ERA conclusions, based on the previous ERA of empagliflozin, remain unchanged. The MAH has provided an updated ERA table, including new calculations for all proposed indications of Jardiance.

2.2.4. 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 empaglifozin.

The non-clinical data provided as part of the application are acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment
Efficacy and safety	1245.137 / c37800399 (EMPA-KIDNEY)	To demonstrate superiority of empagliflozin 10 mg vs. placebo on top of guideline-directed medical therapy	Randomised, placebo-controlled, double-blind, parallel-group	Empagliflozin 10 mg film-coated tablets Placebo tablets matching empagliflozin 10 mg Once daily, oral	Total randomized: 6609 Empagliflozin 10 mg: 3304 Placebo: 3305	Chronic kidney disease at risk of kidney disease progression	Event-driven, median observation about 24 months, exposure about 22 months

2.3.2. Pharmacodynamics

Mechanism of action

The exact mechanisms of SGLT2 inhibitors are not completely understood; however, it has been demonstrated that in addition to glucose lowering, empagliflozin reduces sodium reabsorption in the proximal tubule and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, increasing tubule-glomerular feedback and reducing intra-glomerular pressure, transient natriuresis and increasing urine volume, lowering both pre- and afterload of the heart, downregulating sympathetic activity, and reducing left ventricular wall stress as evidenced by lower NT-proBNP values and beneficial effects on cardiac remodelling, filling pressures and diastolic function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure, and a lowering of uric acid, may further contribute to the beneficial effects.

The proposed mechanism for reno-protective effects are as follows: mechanisms behind the kidney effects of empagliflozin are likely multifactorial, but direct kidney haemodynamic effects are considered to play an important role. Empagliflozin reduces proximal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula densa, which has been shown to activate tubuloglomerular feedback leading to afferent arteriolar vasoconstriction, thereby reducing intraglomerular pressure and urinary albumin excretion.

Primary and secondary pharmacology

There were no new dedicated clinical pharmacology studies. There were no clinical pharmacology analyses in the EMPA-KIDNEY trial.

2.3.3. Discussion on clinical pharmacology

There were no new dedicated clinical pharmacology studies, which is acceptable. There were no clinical pharmacology analyses in the EMPA-KIDNEY trial. The proposed mechanisms of SGLT2 inhibitors with regards to renoprotection are likely multifactorial, but direct kidney haemodynamic effects are considered to play an important role. Empagliflozin reduces proximal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula densa, which has been shown to activate a tubuloglomerular feedback leading to afferent arteriolar vasoconstriction, thereby reducing intraglomerular pressure. Current knowledge on the mechanism of actions of empagliflozin has been sufficiently described.

2.3.4. Conclusions on clinical pharmacology

There were no new dedicated clinical pharmacology studies, which is acceptable. The mechanisms of action of SGLT2 inhibitors for renoprotection are not completely understood but likely related to direct hemodynamic effects leading to a reduction in intraglomerular pressure. Current knowledge on the mechanism of action of empagliflozin has been sufficiently described.

2.4. Clinical efficacy

The clinical efficacy is based on the results of the Phase III pivotal outcome trial 1245.137 (EMPA-KIDNEY).

2.4.1. Dose response studies

No specific dose response studies were performed. The dose for the EMPA-KIDNEY trials was based on previous results from the EMPA-REG trial.

The results of trial 1245.25 (EMPA-REG OUTCOME) in patients with T2DM and established CV disease showed that empagliflozin significantly reduced the risk of 3-point major adverse cardiovascular event (3P-MACE), which was mainly driven by the reduction in CV death. The results were consistent for empagliflozin doses of 10 mg and 25 mg once daily. A *post hoc* analysis of the EMPA-REG OUTCOME trial indicated that empagliflozin significantly reduced the incidence of the composite outcome of doubling of creatinine, the need to start kidney replacement therapy or renal death. These benefits were consistent regardless of baseline use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). In addition, there was no evidence of an increased risk of hyperkalaemia or acute kidney injury. For all cardiovascular, renal, and mortality outcomes assessed in the EMPA-REG OUTCOME trial, risk reductions observed with 10 mg and 25 mg were virtually identical with a similar safety profile. As a result, 10 mg is the only dose being evaluated in other ongoing outcome studies in patients with chronic heart failure. For the EMPA-KIDNEY trial, only the dose of 10 mg was therefore being investigated.

2.4.2. Main study

Study 1245.137 (EMPA-KIDNEY)

The main study was trial 1245.137, also known as EMPA-KIDNEY, a multicentre international randomized parallel group double-blind placebo-controlled clinical trial of empagliflozin once daily to assess cardio-renal outcomes in patients with chronic kidney disease.

Methods

Study participants

Key **inclusion criteria** were:

- Age was ≥18 years at time of Screening
- Evidence of progressive CKD at risk of kidney disease progression.
  This was based on local laboratory results recorded at least 3 months before and at the time of the Screening visit, and required that:
    - CKD-EPI eGFR ≥20 <45 mL/min/1.73m^2; or
    - CKD-EPI eGFR ≥45 <90 mL/min/1.73m2 with urinary albumin:creatinine ratio ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g).
- Treatment with appropriate doses of single agent RAS-inhibition with either ACEi or ARB unless such treatment was either not tolerated or not indicated.

Note: the number of participants with or without diabetes mellitus (of any type) was to be at least one-third of each, and the number of participants with an eGFR >45 mL/min/1.73m2 limited to about one-third.

Key **exclusion criteria** were

- Currently receiving SGLT-2 or SGLT-1/2 inhibitor
- Diabetes mellitus type 2 and prior atherosclerotic cardiovascular disease with an eGFR >60 mL/min/1.73m2 at time of Screening
- Receiving combined ACEi and ARB treatment
- Maintenance dialysis, functioning kidney transplant, or scheduled living donor transplant
- Polycystic kidney disease
- Symptomatic hypotension, or systolic blood pressure <90 or >180 mmHg at time of Screening
- Any immunosuppression therapy in the last 3 months (except prednisolone ≤10 mg or equivalent); or anyone currently on >10 mg prednisolone (or equivalent)

In addition, individuals were to be excluded at the Randomization visit if the participant did not adhere to run-in treatment, was no longer willing to be randomized and followed for at least 3 years, was considered by a local investigator not to be suitable for randomization, or experienced ketoacidosis, heart attack, stroke, or hospitalization for heart failure, or hospitalization for urinary tract infection or acute kidney injury during run-in.

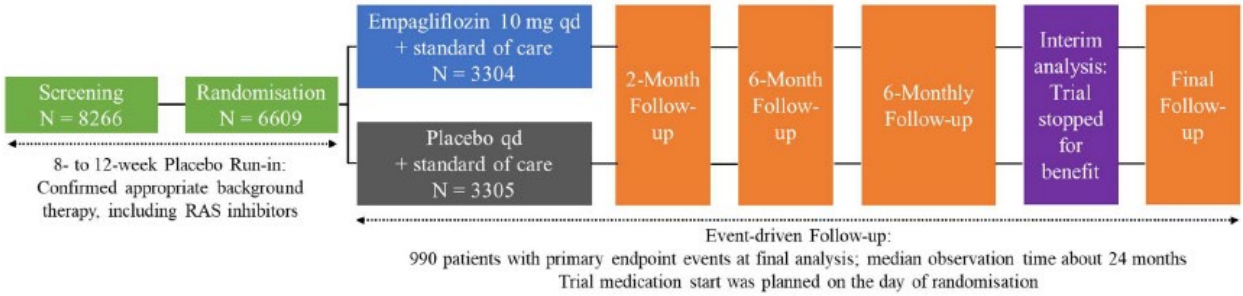
Treatments

This was a multicentre international randomised parallel group double-blind placebo-controlled clinical trial of empagliflozin 10 mg once daily on top of background therapy, including RASi to assess cardio-renal outcomes in patients with chronic kidney disease.

Prior to randomisation, potentially eligible participants entered an 8-12 week 'Run-in' period, during which they received single-blind placebo tablets. The main purpose of the Run-in period was to help ensure that only those likely to continue taking study treatment for an extended period were randomised (see Figure 1). It also provided time to confirm inclusion criteria based on the local samples taken at the Screening Visit, and provided investigators with an opportunity to review and approve the participation of each patient and to ensure they were on appropriate background therapy (including RAS inhibitors). Eligible and

consenting individuals attending the Randomisation Visit were allocated to empagliflozin 10 mg or placebo in a 1:1 ratio using a minimised randomisation algorithm that helps to ensure balance between the treatment groups with respect to the following prognostic variables: age, sex, prior diabetes, eGFR and UACR (both based on local laboratory results at screening), and region. Following randomisation, participants were scheduled to attend Follow-up visits at 2 and 6 months, and then 6-monthly until the end of the trial.

Figure 1. Design of the EMPA-KIDNEY trial



In general, baseline was defined as the last available measurement on or prior to the day of randomisation (excluding any pre-screening measurements). Trial medication start was planned on the day of randomisation and baseline assessments were to be taken prior to any intake of trial medication.

One tablet was to be taken daily with or without food. To ensure a dose interval of about 24 hours, instructions were provided to participants suggesting the medication was ideally to be taken at approximately the same time every day.

Objectives

The primary aim was to assess the effect of empagliflozin on time to kidney disease progression or CV death. The key secondary aims were to assess the effect of empagliflozin on time to HHF or CV death, occurrences of hospitalisations from any cause, and time to death from any cause. Other assessments, including analyses of safety, were also planned.

Outcomes/endpoints

The following endpoints were defined for the EMPA-KIDNEY trial:

Primary endpoint:

The primary endpoint was a composite of

- time to kidney disease progression, defined as the first occurrence of any of the following:
  - end stage kidney disease [ESKD*],
  - a sustained decline in eGFR to <10 mL/min/1.73 m2,
  - 'as adjudicated' renal death, or
  - a sustained decline of ≥40% in eGFR from randomization
- CV death ('as adjudicated')

Secondary endpoints:

Key secondary endpoints (confirmatory):

- time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated')
- time to occurrences of all-cause hospitalisations (first and recurrent combined)
- time to death from any cause ('as adjudicated')

Other secondary endpoints (exploratory):

- time to the first occurrence of kidney disease progression
- time to CV death ('as adjudicated')
- time to first occurrence of CV death ('as adjudicated') or ESKD*

*ESKD was defined as the initiation of maintenance dialysis or receipt of a kidney transplant. Dialysis was considered as maintenance if it was required for ≥90 days or if the dialysis was stopped within 90 days for a reason of 'received kidney transplant', 'dialysis is futile' or 'subject refused dialysis'. Dialysis ongoing at the last scheduled trial follow-up visit or the last scheduled visit before death^, withdrawal of consent or loss to follow-up was also considered as maintenance irrespective of duration. Where changes in dialysis modality were consecutive with one another durations were summed for determining whether the maintenance duration had been met.

^ For deaths within 90 days of starting dialysis an adjudicator was asked to consider whether the dialysis would have been required long-term or only temporarily; if temporary then the outcome of dialysis was to be changed from 'ongoing' to 'stopped for other reason' and not considered as an ESKD event.

To meet the requirement for a 'sustained' decline in eGFR, this was defined as either:

- measured at 2 consecutive scheduled trial follow-up visits (at least 30 days apart); or
- measured at the last scheduled trial follow-up visit or the last scheduled visit before death, withdrawal of consent or loss to follow-up.

Sample size

The trial was planned to randomise approximately 6000 participants from about 200-250 sites and to continue until a minimum of 1070 primary outcome events has occurred. Such an event-driven trial would provide an overall power of 90% at p = 0.05 (2-sided) to detect an 18% relative reduction in the primary outcome (time to kidney disease progression or CV death). During the trial, the Steering Committee monitored event rates for the primary outcome and its components blind to treatment allocation, and if necessary, could consider proposing changes to the protocol.

Randomisation

Eligible and consenting individuals were allocated empagliflozin or matching placebo using a minimisation approach via a randomisation program on the trial computer-based system. The algorithm included a stochastic element (treatment was assigned to the arm determined by the minimisation algorithm with a probability of 0.9 and by a random number generator with a probability of 0.1). Given the stochastic element of the randomisation, rerandomisation methods for the analysis were not considered necessary and only traditional methods of analysis were planned. Randomised participants were to be issued with a 7-month supply of study treatment consisting of empagliflozin 10 mg or matching placebo.

Blinding (masking)

Participants, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (apart from the DMC) remained blinded with regard to the randomised treatment assignments.

During the trial, unblinded analyses of all Serious Adverse Events (SAEs) and other trial outcomes, both overall and in key subgroups, including by region, and all SSARs were supplied in strict confidence to the independent DMC. The unblinded Independent Statistician for the DMC was responsible for generating and providing these unblinded reports.

A central panel of clinicians based at, or overseen by, the CCO was responsible for the adjudication of all deaths and events initially reported as HHF, MI, stroke, liver injury, ketoacidosis, lower limb amputation, genital infections, and acute kidney injury as specified in the respective SOP. The members of that panel, and all staff involved in preparing the documents reviewed by the panel, remained blinded for the adjudication.

Statistical methods

The trial was designed to have a power of 90% for the primary endpoint at a 2-sided α of 0.05 to detect an 18% relative reduction in the primary outcome, which required approximately 1070 primary outcome events.

The final analysis of the primary endpoint was performed at a 2-sided α of 0.0017. If the confirmatory primary endpoint was significant, the formal statistical testing of the key secondary endpoints was performed via the Hochberg procedure, preserving the trial's overall type I error rate, starting with a 2-sided α of 0.0290. The significance levels were predefined according to α-spending functions based on the number of primary outcome events observed at the time of the DMC interim analysis.

Unless otherwise specified, efficacy analyses followed the ITT principle and included all randomised patients (RS; treatment assigned as randomised) and all available data from the follow-up period (OC-AD); data occurring after the final follow-up visit were not considered.

Adjudication was performed for all deaths and events initially reported as HHF, myocardial infarction, stroke, liver injury, ketoacidosis, lower limb amputation, genital infections, and acute kidney injury. A central panel of responsible clinicians remained blinded for the adjudication.

The primary and secondary time-to-event endpoints were analysed using a Cox proportional hazards regression model with factors of treatment (empagliflozin, placebo) and each of the variables used in the minimisation algorithm for randomisation. This model was used to test the equality of the hazard rates via the Wald test for the treatment effect. The same model was used to estimate the HR of the treatment effect and the corresponding asymptotic 2-sided 95% Wald confidence interval (CI). Cumulative incidence function and/or Kaplan-Meier curves were also produced to summarise the primary endpoint data. Sensitivity analyses were performed to testing the influence of the source of eGFR data (central or local); omitting the randomisation minimisation factors; missing data imputation; competing risk of non-CV/renal death (Fine-Gray); COVID-19 AEs.

Results

Participants

Table 6. Disposition of participants – SCR

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Screened			8266
Randomised	3305 (100.0)	3304 (100.0)	6609 (100.0)
Completed trial or died[1]	3287 (99.5)	3281 (99.3)	6568 (99.4)
Died	167 (5.1)	148 (4.5)	315 (4.8)
Prematurely discontinued trial	18 (0.5)	23 (0.7)	41 (0.6)
Lost to follow-up[2]	9 (0.3)	9 (0.3)	18 (0.3)
Consent withdrawn	9 (0.3)	14 (0.4)	23 (0.3)
Treated	3305 (100.0)	3304 (100.0)	6609 (100.0)
Completed treatment	2457 (74.3)	2549 (77.1)	5006 (75.7)
Prematurely discontinued study medication	848 (25.7)	755 (22.9)	1603 (24.3)
Study drug stopped, reason missing[3]	337 (10.2)	295 (8.9)	632 (9.6)
Adverse event	248 (7.5)	236 (7.1)	484 (7.3)
Serious fatal events	129 (3.9)	120 (3.6)	249 (3.8)
Non-fatal events	119 (3.6)	116 (3.5)	235 (3.6)
Other reason	263 (8.0)	224 (6.8)	487 (7.4)
Participant wishes	89 (2.7)	68 (2.1)	157 (2.4)
Doctor advice	38 (1.1)	40 (1.2)	78 (1.2)
Participant concerned about study treatment	23 (0.7)	28 (0.8)	51 (0.8)
Contraindicated drug started	32 (1.0)	18 (0.5)	50 (0.8)
Cannot attend clinic because moving out of the area	15 (0.5)	9 (0.3)	24 (0.4)
Cannot attend clinic because of personal problems	8 (0.2)	16 (0.5)	24 (0.4)
Other[4]	58 (1.8)	45 (1.4)	103 (1.6)

1 Defined as all participants with a primary event or follow-up for the primary endpoint until study end/death.

2 Other participants with incomplete follow-up for the primary endpoint.

3 Participants who recorded a treatment stop date >1 day prior to the final follow-up visit were considered as early treatment discontinuations.

4 Other reasons included any category with a frequency <20 participants in total.

Recruitment

This trial was a multicentre trial conducted in 8 countries across North America, Europe, and Asia. Of the 8266 screened participants, 1657 were not randomised; most commonly because of ineligible screening lab results.

Table 7. Reason for not randomising screened patients – SCR

	Total N (%)
Included in screened set	8266
Included in randomised set	6609
Not randomised	1657 (100.0)
Ineligible at screening	82 (4.9)
Inclusion / exclusion criteria not met*	82 (4.9)
Immunosuppression therapy in last 3 months (except prednisolone <=10 mg or equivalent) or on >10 mg prednisolone (or equivalent)	21 (1.3)
Relevant concomitant diagnoses	18 (1.1)
DM type 2 and prior atherosclerotic CV disease with screening eGFR>60	17 (1.0)
Receiving combined ACEi and ARB treatment	10 (0.6)
Treatment with any SGLT-2 inhibitor or SGLT-1 and 2 inhibitor	6 (0.4)
Necessary blood and urine samples could not be taken	5 (0.3)
IV immunosuppression therapy in last 3 months or on >45 mg prednisolone (or equivalent)	3 (0.2)
Type 1 diabetes	3 (0.2)
Consent withdrawn	0

* Patients may have not met more than one in/exclusion criterion.

Conduct of the study

The trial has been completed (first patient screened 01 Feb 2019, last patient completed 05 Jul 2022). The trial was carried out in compliance with the clinical trial protocol, in accordance with the principles of the Declaration of Helsinki, in accordance with ICH GCP, and in accordance with applicable regulatory requirements and the Applicant's standard operating procedures.

The EMPA-KIDNEY trial was carried out at 241 clinical sites in 8 countries in North America, Europe, and Asia (United States, Canada, Germany, United Kingdom, Italy, China, Malaysia, and Japan).

If knowledge of the actual treatment of a participant was required to provide appropriate medical treatment or to assure the safety of trial participants, investigators could request emergency unblinding of the treatment allocation. During this trial, the medication code was broken for 3 participants. The medication code for one participant was broken by the investigator due to adverse events. The medication codes for the 2 other participants were broken by the investigators due to other medical reasons.

Before the COVID-19 outbreak, 2848 of 6609 participants had been randomised in this trial, and 3761 participants were randomised thereafter.

The overall proportion of participants with important protocol deviations was similar between the treatment groups. The most common important protocol deviation was clustered/short visits, with data not entered in real-time.

Table 8. Number of participants with important protocol deviations – RS

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Number of participants	3305 (100.0)	3304 (100.0)	6609 (100.0)
Participants with at least one important protocol deviation	41 (1.2)	43 (1.3)	84 (1.3)
Study-specific analysis	28 (0.8)	32 (1.0)	60 (0.9)
Clustered/short visits, data not entered in real-time	28 (0.8)	32 (1.0)	60 (0.9)
Entrance criteria not met	8 (0.2)	10 (0.3)	18 (0.3)
No CKD at risk of progression	6 (0.2)	6 (0.2)	12 (0.2)
Other entrance criteria not met	2 (0.1)	4 (0.1)	6 (0.1)
History of ketoacidosis	1 (<0.1)	1 (<0.1)	2 (<0.1)
Relevant concomitant diagnoses	0 (0.0)	1 (<0.1)	1 (<0.1)
Previous or scheduled bariatric surgery	1 (<0.1)	1 (<0.1)	2 (<0.1)
IV immunosuppression therapy in last 3 months or on >45 mg prednisone (or equivalent)	0 (0.0)	1 (<0.1)	1 (<0.1)
Incorrect trial medication taken	3 (0.1)	0	3 (<0.1)
Other	2 (0.1)	1 (<0.1)	3 (<0.1)

A participant could have had more than one important protocol deviation.

Baseline data

Approximately two-thirds of the participants (66.8%) were men, 58.4% of participants were White, 54.6% of the participants were ≥65 years old, including 23.0% of participants ≥75 years old.

Table 9. Demographic data – RS

	Placebo	Empa 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Sex, N (%)			
Male	2210 (66.9)	2207 (66.8)	4417 (66.8)
Female	1095 (33.1)	1097 (33.2)	2192 (33.2)
Race (summary), N (%)			
White	1920 (58.1)	1939 (58.7)	3859 (58.4)
Asian	1199 (36.3)	1194 (36.1)	2393 (36.2)
Black or African American	134 (4.1)	128 (3.9)	262 (4.0)
Other including mixed race	52 (1.6)	43 (1.3)	95 (1.4)
Ethnicity[1], N (%)			
Not Hispanic/Latino	723 (21.9)	708 (21.4)	1431 (21.7)
Hispanic/Latino	119 (3.6)	103 (3.1)	222 (3.4)
Region, N (%)			
North America	873 (26.4)	844 (25.5)	1717 (26.0)
Europe	1304 (39.5)	1344 (40.7)	2648 (40.1)
Japan	308 (9.3)	304 (9.2)	612 (9.3)
Other Asia	820 (24.8)	812 (24.6)	1632 (24.7)
Age [years], mean (SD)	63.3 (13.9)	63.4 (13.9)	63.3 (13.9)
<65, N (%)	1501 (45.4)	1501 (45.4)	3002 (45.4)
<50	580 (17.5)	561 (17.0)	1141 (17.3)
50 to <65	921 (27.9)	940 (28.5)	1861 (28.2)
≥65, N (%)	1804 (54.6)	1803 (54.6)	3607 (54.6)
65 to <75	1044 (31.6)	1045 (31.6)	2089 (31.6)
≥75	760 (23.0)	758 (22.9)	1518 (23.0)
Smoking status [N (%)]			
Smokes regularly	354 (10.7)	326 (9.9)	680 (10.3)
No longer smokes regularly	1131 (34.2)	1138 (34.4)	2269 (34.3)
No	1820 (55.1)	1839 (55.7)	3659 (55.4)
Alcohol status [N, (%)]			
Drinks regularly	647 (19.6)	621 (18.8)	1268 (19.2)
No longer drinks regularly	675 (20.4)	731 (22.1)	1406 (21.3)
No	1983 (60.0)	1951 (59.0)	3934 (59.5)

[1]Ethnicity was recorded only for sites in the US or Canada.
Participants with information missing are not shown; see source table for the data

The mean eGFR at baseline was 37.3 (SD 14.45) mL/min/1.73 m2. A total of 34.5% of participants had an eGFR <30 mL/min/1.73 m2, 44.3% had an eGFR ≥30 and <45, 13.4% had an eGFR ≥45 and <60, and 7.7% had an eGFR ≥60. The median UACR was 329.4 mg/g (Q1, Q3 48.5, 1068.9). Normal UACR was reported for 20.1% of participants, while 28.2% had microalbuminuria and 51.7% had macroalbuminuria. 54.0% of the participants were non-diabetic, 44.4% had T2DM, 1.0% had T1DM, and the diabetes status was unknown or missing for 0.5%. The primary cause of kidney disease was diabetes (31.1%), followed by glomerular disease (25.3 %), and hypertensive/renovascular disease (21.9%). About one-quarter of participants had prior CV diseases (26.7%), and 10.0% had prior HF.

Table 10. Baseline characteristics – RS

	Placebo	Empa 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
eGFR [mL/min/1.73 m^2], mean (SD)	37.26 (14.42)	37.37 (14.48)	37.32 (14.45)
<30, N (%)	1151 (34.8)	1131 (34.2)	2282 (34.5)
≥30 to <45, N (%)	1461 (44.2)	1467 (44.4)	2928 (44.3)
≥45 to <60, N (%)	442 (13.4)	446 (13.5)	888 (13.4)
≥60, N (%)	251 (7.6)	260 (7.9)	511 (7.7)
UACR [mg/g], median (Q1, Q3)	327.26 (53.54, 1073.96)	330.58 (46.29, 1061.34)	329.35 (48.53, 1068.93)
Normal (<30), N (%)	663 (20.1)	665 (20.1)	1328 (20.1)
Microalbuminuria (≥30 to ≤300), N (%)	937 (28.4)	927 (28.1)	1864 (28.2)
Macroalbuminuria (>300), N (%)	1705 (51.6)	1712 (51.8)	3417 (51.7)
KDIGO risk category, N (%)			
Low risk	2 (0.1)	2 (0.1)	4 (0.1)
Moderately increased risk	115 (3.5)	140 (4.2)	255 (3.9)
High risk	716 (21.7)	697 (21.1)	1413 (21.4)
Very high risk	2472 (74.8)	2465 (74.6)	4937 (74.7)
NT-proBNP [pg/mL], median (Q1, Q3)	158.5 (67.7, 417.4)	162.0 (70.0, 421.2)	160.3 (69.0, 419.1)
<110, N (%)	1265 (38.3)	1245 (37.7)	2510 (38.0)
≥110 to <330, N (%)	1028 (31.1)	1033 (31.3)	2061 (31.2)
≥330, N (%)	980 (29.7)	996 (30.1)	1976 (29.9)
HbA1c [mmol/mol], mean (SD)	45.0 (13.7)	45.0 (13.5)	45.0 (13.6)
<39, N (%)	1353 (40.9)	1329 (40.2)	2682 (40.6)
≥39 to <48, N (%)	897 (27.1)	940 (28.5)	1837 (27.8)
≥48, N (%)	999 (30.2)	977 (29.6)	1976 (29.9)
Haematocrit [%], mean (SD)	39.1 (5.1)	39.1 (5.1)	39.1 (5.1)
<37, N (%)	911 (27.6)	907 (27.5)	1818 (27.5)
≥37 to < 41, N (%)	943 (28.5)	948 (28.7)	1891 (28.6)
≥41, N (%)	1124 (34.0)	1127 (34.1)	2251 (34.1)

Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
SBP [mmHg], mean (SD)	136.7 (18.4)	136.4 (18.1)	136.5 (18.3)
<130, N (%)	1208 (36.6)	1190 (36.0)	2398 (36.3)
≥130 to <145, N (%)	1063 (32.2)	1126 (34.1)	2189 (33.1)
≥145, N (%)	1034 (31.3)	988 (29.9)	2022 (30.6)
DBP [mmHg], mean (SD)	78.1 (11.9)	78.1 (11.7)	78.1 (11.8)
<75, N (%)	1286 (38.9)	1294 (39.2)	2580 (39.0)
≥75 to <85, N (%)	1033 (31.3)	1019 (30.8)	2052 (31.0)
≥85, N (%)	986 (29.8)	991 (30.0)	1977 (29.9)
BMI [kg/m^2], mean (SD)	29.8 (6.8)	29.7 (6.7)	29.7 (6.8)
<25, N (%)	821 (24.8)	798 (24.2)	1619 (24.5)
≥25 to <30, N (%)	1140 (34.5)	1157 (35.0)	2297 (34.8)
≥30, N (%)	1337 (40.5)	1340 (40.6)	2677 (40.5)
Waist circumference [cm], mean (SD)	102.7 (17.1)	102.8 (17.3)	102.7 (17.2)
Hip circumference [cm], mean (SD)	107.2 (14.9)	107.3 (14.8)	107.3 (14.8)
Baseline diabetes status[1], N (%)			
Non-diabetic	1790 (54.2)	1779 (53.8)	3569 (54.0)
Diabetic	1515 (45.8)	1525 (46.2)	3040 (46.0)
Type 1 DM	34 (1.0)	34 (1.0)	68 (1.0)
Type 2 DM	1466 (44.4)	1470 (44.5)	2936 (44.4)
Other/Unknown	15 (0.5)	21 (0.6)	36 (0.5)
Time since DM diagnosis [years], N (%)			
≤1	38 (1.1)	39 (1.2)	77 (1.2)
>1 to <5	138 (4.2)	148 (4.5)	286 (4.3)
≥5 to 10	250 (7.6)	253 (7.7)	503 (7.6)
>10	1046 (31.6)	1035 (31.3)	2081 (31.5)
Primary cause of kidney disease, N (%)			
Diabetic	1025 (31.0)	1032 (31.2)	2057 (31.1)
Glomerular	816 (24.7)	853 (25.8)	1669 (25.3)
Hypertensive/renovascular	739 (22.4)	706 (21.4)	1445 (21.9)
Other/unknown	725 (21.9)	713 (21.6)	1438 (21.8)
Prior CV disease[2], N (%)	904 (27.4)	861 (26.1)	1765 (26.7)
Myocardial infarction	351 (10.6)	351 (10.6)	702 (10.6)
Heart failure	334 (10.1)	324 (9.8)	658 (10.0)
Peripheral arterial disease	226 (6.8)	244 (7.4)	470 (7.1)
Stroke	215 (6.5)	190 (5.8)	405 (6.1)
Transient ischaemic attack	180 (5.4)	152 (4.6)	332 (5.0)

All baseline laboratory parameters were assessed centrally, with the exception of locally assessed haematocrit. Local data were used for eGFR and UACR if central baseline data missing.

KDIGO = Kidney Disease Improving Global Outcomes (risk category from 2020 guideline); [P20-09106]

[1] Baseline diabetes status defined as participant-reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA1c ≥48 mmol/mol. If type of diabetes was missing from participant-reported history or the instance of diabetes was not from participant-reported history, it was assumed to be type 2 diabetes.

[2] Baseline disease considered present if observed in participant-reported history or as an AE during the run-in period.

Participants with information missing are not shown; see source table for the full data.

Table 11. Demographic and baseline characteristics by baseline diabetes status – RS

	Without diabetes		With diabetes	
	Placebo	Empa 10 mg	Placebo	Empa 10 mg
Number of patients, N (%)	1790 (100.0)	1799 (100.0)	1515 (100.0)	1525 (100.0)
Female	598 (33.4)	598 (33.6)	497 (32.8)	499 (32.7)
White	1043 (58.3)	1006 (56.5)	877 (57.9)	933 (61.2)
Asian	682 (38.1)	703 (39.5)	517 (34.1)	491 (32.2)
Black or African American	41 (2.3)	48 (2.7)	93 (6.1)	80 (5.2)
Age [years], mean (SD)	59.1 (15.3)	59.6 (15.4)	68.2 (9.8)	67.9 (10.1)
eGFR [mL/min/1.73 m^2], mean (SD)	38.77 (15.24)	38.47 (15.07)	35.47 (13.16)	36.10 (13.65)
<30, N (%)	569 (31.8)	562 (31.6)	582 (38.4)	569 (37.3)
≥30 to <45, N (%)	774 (43.2)	783 (44.0)	687 (45.3)	684 (44.9)
≥45, N (%)	447 (25.0)	434 (24.4)	246 (16.2)	272 (17.8)
UACR [mg/g], median (Q1, Q3)	392.23 (71.47, 1053.86)	368.61 (52.09, 997.38)	251.63 (38.40, 1108.11)	270.96 (42.47, 1171.50)
Normal (<30), N (%)	328 (18.3)	353 (19.8)	335 (22.1)	312 (20.5)
Microalbuminuria (≥30 to ≤300), N (%)	467 (26.1)	454 (25.5)	470 (31.0)	473 (31.0)
Macroalbuminuria (>300), N (%)	995 (55.6)	972 (54.6)	710 (46.9)	740 (48.5)
KDIGO risk category, N (%)				
Low risk	1 (0.1)	0	1 (0.1)	2 (0.1)
Moderately increased risk	77 (4.3)	92 (5.2)	38 (2.5)	48 (3.1)
High risk	401 (22.4)	386 (21.7)	315 (20.8)	311 (20.4)
Very high risk	1311 (73.2)	1301 (73.1)	1161 (76.6)	1164 (76.3)
Primary cause of kidney disease, N (%)				
Diabetic	0	0	1025 (67.7)	1032 (67.7)
Glomerular	737 (41.2)	760 (42.7)	79 (5.2)	93 (6.1)
Hypertensive/renovascular	530 (29.6)	513 (28.8)	209 (13.8)	193 (12.7)
Other/unknown	523 (29.2)	506 (28.4)	202 (13.3)	207 (13.6)
Prior CV disease[1], N (%)				
Myocardial infarction	121 (6.8)	134 (7.5)	230 (15.2)	217 (14.2)
Heart failure	120 (6.7)	106 (6.0)	214 (14.1)	218 (14.3)
Peripheral arterial disease	75 (4.2)	77 (4.3)	151 (10.0)	167 (11.0)
Stroke	79 (4.4)	75 (4.2)	136 (9.0)	115 (7.5)
Transient ischaemic attack	65 (3.6)	64 (3.6)	115 (7.6)	88 (5.8)
Use of ACEi/ARBs, N (%)	1506 (84.1)	1531 (86.1)	1291 (85.2)	1300 (85.2)
Use of diuretics, N (%)	597 (33.4)	554 (31.1)	856 (56.5)	808 (53.0)
Use of beta-blockers, N (%)	590 (33.0)	599 (33.7)	775 (51.2)	797 (52.3)
Use of diabetes drugs, N (%)	0	0	1344 (88.7)	1351 (88.6)

All baseline laboratory parameters were assessed centrally, with the exception of locally assessed haematocrit. Local data were used for eGFR and UACR if central baseline data missing.

[1] Baseline disease considered present if observed in patient-reported history or as an AE during the run-in period.

Concomitant therapies at baseline were balanced across the treatment groups. A total of 85.2% of participants used RAS-inhibitors at baseline.

The proportion of participants who used diuretics during follow-up increased to 46.7% vs. 41.8% at baseline in the placebo group, while it remained almost the same in the empagliflozin group (41.2% vs. 41.8%). The increases in use of RAS-inhibitors, betablockers, and drugs for diabetes during the follow-up were comparable between treatment groups.

Table 12. Baseline non-study medications of interest – RS

	Placebo	Empa 10 mg	Total
Number of participants	3305 (100.0)	3304 (100.0)	6609 (100.0)
RAS-inhibitors, N (%)	2797 (84.6)	2831 (85.7)	5628 (85.2)
Diuretics, N (%)	1453 (44.0)	1362 (41.2)	2815 (42.6)
Beta-blockers, N (%)	1365 (41.3)	1396 (42.3)	2761 (41.8)
Drugs used in diabetes, N (%)	1344 (40.7)	1351 (40.9)	2695 (40.8)

RAS-inhibitors defined according to the WHO-DD SDGs of ACEIs, ARBs and renin inhibitors and BIcDQ ARNIs.
Beta-blockers, diuretics and drugs used in diabetes defined according to the user-defined 'Drugsman' coding dictionary.

Numbers analysed

All randomised participants were dispensed study medication and therefore included in the treated set (TS.).

Table 13. Patient analysis sets – RS

		Placebo	Empa 10mg	Total
Included in Randomised set (RS)	N (% of RS)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Included in Treated set (TS)	N (% of RS)	3305 (100.0)	3304 (100.0)	6609 (100.0)

Outcomes and estimation

Primary endpoint (Time to Kidney disease progression or CV death)

Kidney disease progression or CV death events occurred in a lower proportion of participants in the empagliflozin group in comparison to the placebo group. The risk of kidney disease progression or CV death was significantly reduced by 28% with empagliflozin treatment compared with placebo (HR 0.72; 99.83% CI 0.59, 0.89). No renal deaths as part of the composite endpoint occurred.

Table 14. Time to the first event of kidney disease progression or adjudicated CV death, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	558 (16.9)	432 (13.1)
Kidney disease progression as the first event[1]	504 (15.2)	384 (11.6)
ESKD only	63 (1.9)	47 (1.4)
eGFR reduction <10 mL/min/1.73 m² and ≥40%	67 (2.0)	43 (1.3)
eGFR reduction to <10 mL/min/1.73 m² only	1 (<0.1)	1 (<0.1)
eGFR reduction ≥40% only	373 (11.3)	293 (8.9)
CV death as the first event	54 (1.6)	48 (1.5)
Incidence rate per 100 years at risk (95% CI)	8.96 (8.23, 9.72)	6.85 (6.22, 7.51)
Hazard ratio vs. placebo (95% CI)		0.72 (0.64, 0.82)
(99.83% CI)[2]		(0.59, 0.89)
p-value		<0.0001

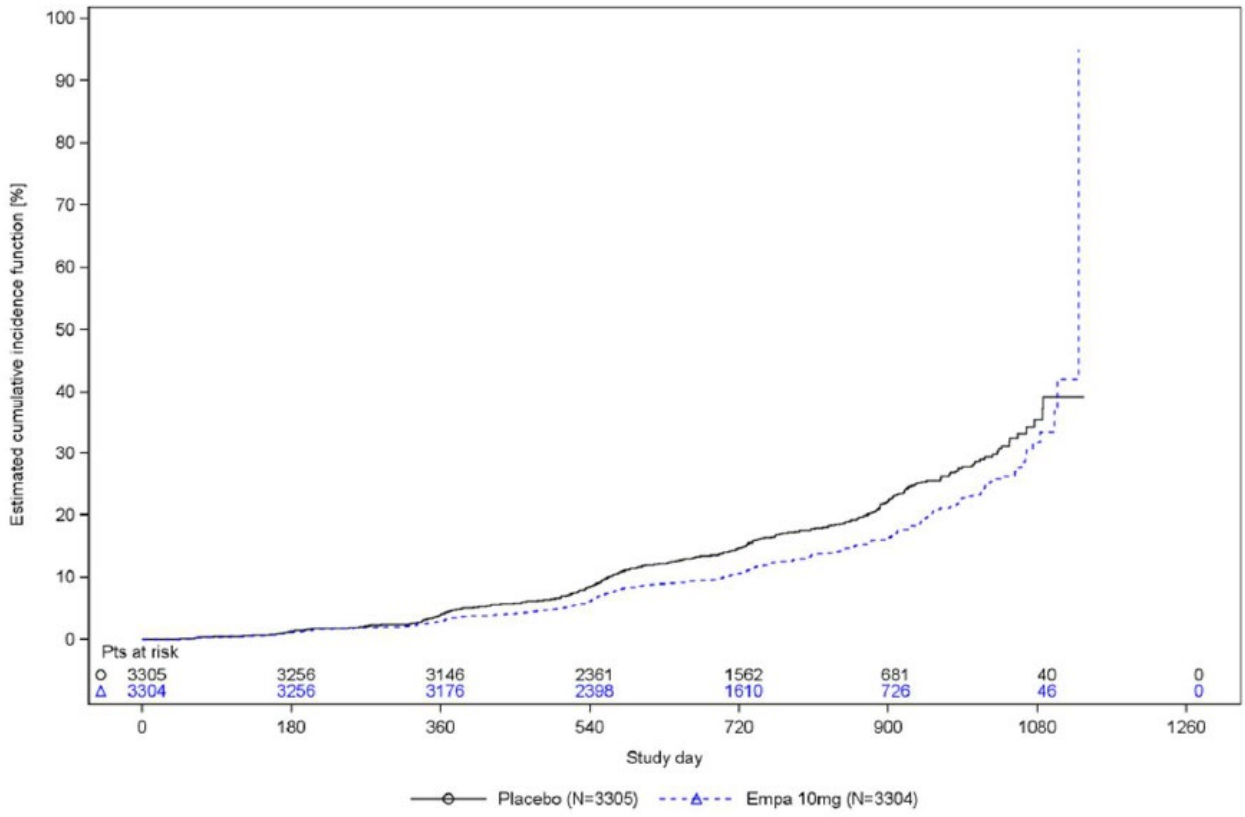
Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

[1] Where there were multiple components contributing to the endpoint these occurred on the same day.

[2] 99.83% CI, corresponding to a 2-sided significance level of <0.0017 required to claim superiority.

The separation of the estimated cumulative incidence of kidney disease progression or CV death between empagliflozin and placebo became evident approximately 1 year after randomisation and continued over time until the number of participants at risk became too low to provide stable estimates.

Figure 2. Time to the first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function (considering non- CV/renal death as a competing risk) – RS



Key secondary endpoints (Hochbergtesting)

As the analysis of the primary endpoint was statistically significant (p<0.0017), confirmatory statistical testing of the key secondary endpoints was performed. The order of testing the key secondary endpoints and the 2-sided significance levels were determined through the Hochberg procedure; testing was performed in the order of the observed p-values, from largest to smallest. The required significance level for the first key secondary endpoint was p<0.0290; for the second endpoint, p<0.0145 (if first non-significant), and p<0.0097 for the third endpoint (if second non-significant).

- **Time to occurrence of all-cause hospitalisation, first and recurrent combined**

All-cause hospitalisations occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The total number of hospitalisations events (first and recurrent) was also lower in the empagliflozin group than in the placebo group. The risk of all-cause hospitalisations was significantly reduced for empagliflozin vs. placebo (Table 15).

Table 15. Time to all-cause hospitalisations (first and recurrent combined) and adjudicated death, joint frailty model – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Total number of hospitalisations, N	1895	1611
Participants with all-cause hospitalisations then adjudicated death, N (%)	136 (4.1)	120 (3.6)
Participants with all-cause hospitalisations only, N (%)	899 (27.2)	840 (25.4)
Participants with adjudicated death only, N (%)	31 (0.9)	28 (0.8)
Hazard ratio vs. placebo of all-cause hospitalisations (95% CI) (99.03% CI)[1]		0.86 (0.78, 0.95) (0.75, 0.98)
p-value		0.0025
Hazard ratio vs. placebo of adjudicated death (95% CI)		0.93 (0.68, 1.26)

Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, log (local screening UACR), local screening eGFR, treatment, sex, screening diabetes status (2 cat.), region, estimated dependence between all-cause hospitalisation and adjudicated death (alpha) (2.43) and variance of frailty (omega) (1.96).

[1] 99.03% CI, corresponding to a 2-sided significance level of <0.0097 required to claim superiority

The mean cumulative incidence of all-cause hospitalisations in the empagliflozin and placebo groups started to diverge shortly after randomisation and continued to separate over time.

- **Time to first occurrence of HHF or CV death**

Although HHF or CV death occurred in a lower proportion of participants in the empagliflozin group than in the placebo group, the risk of HHF or CV death was not significantly reduced with empagliflozin as compared with placebo (Table 16).

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	152 (4.6)	131 (4.0)
HHF as the first event	107 (3.2)	87 (2.6)
CV death as the first event	45 (1.4)	43 (1.3)
Both on the same day	0	1 (<0.1)
Incidence rate per 100 years at risk (95% CI)	2.37 (2.01, 2.77)	2.04 (1.70, 2.40)
Hazard ratio vs. placebo (95% CI)		0.84 (0.67, 1.07)
(98.55% CI)[1]		(0.63, 1.13)
p-value		0.1530

Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

[1] 98.55% CI, corresponding to a 2-sided significance level of <0.0145 required to claim superiority

- **Time to adjudicated death from any cause**

All-cause death occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The risk of all-cause death was not significantly reduced with empagliflozin treatment as compared with placebo.

Table 17. Time to adjudicated death from any cause, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	167 (5.1)	148 (4.5)
Incidence rate per 100 years at risk (95% CI)	2.58 (2.20, 2.98)	2.28 (1.93, 2.66)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.08)
(97.10% CI)[1]		(0.68, 1.11)
p-value		0.2137

Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

[1] 97.10% CI, corresponding to a 2-sided significance level of <0.0290 required to claim superiority

Other secondary endpoints

- **Time to first occurrence of kidney disease progression**

Kidney disease progression occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The risk of kidney disease progression was reduced with empagliflozin treatment vs. placebo.

Table 18. Time to first occurrence of kidney disease progression, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	504 (15.2)	384 (11.6)
Incidence rate per 100 years at risk (95% CI)	8.09 (7.40, 8.81)	6.09 (5.50, 6.72)
Hazard ratio vs. placebo (95% CI)		0.71 (0.62, 0.81)
p-value		<0.0001

Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

- **Time to adjudicated CV death**

Adjudicated CV death occurred in a low proportion of participants in both treatment groups. There was no strong evidence of a treatment difference between empagliflozin and placebo.

Table 19. Time to adjudicated CV death, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	69 (2.1)	59 (1.8)
Incidence rate per 100 years at risk (95% CI)	1.06 (0.83, 1.33)	0.91 (0.69, 1.15)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.19)
p-value		0.3366

Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

- **Time to first occurrence of adjudicated CV death or ESKD**

CV death or ESKD occurred in a lower proportion of participants in the empagliflozin group than in the placebo group. The risk of CV death or ESKD was reduced with empagliflozin treatment vs. placebo.

Table 20. Time to adjudicated CV death or ESKD, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with event, N (%)	217 (6.6)	163 (4.9)
ESKD only	158 (4.8)	108 (3.3)
CV death only	59 (1.8)	55 (1.7)
Incidence rate per 100 years at risk (95% CI)	3.40 (2.96, 3.87)	2.54 (2.16, 2.94)
Hazard ratio vs. placebo (95% CI)		0.73 (0.59, 0.89)
p-value		0.0023

Cox regression model included factors age, sex, baseline diabetes status, local screening eGFR, local screening UACR, region and treatment.

Exploratory endpoints

- **Time-to-event renal endpoints**

The risk of all further time-to-event endpoints with renal components was reduced with empagliflozin treatment compared with placebo, with all upper 95% CIs below 1.

Table 21. Time to renal outcomes, Cox regression – RS

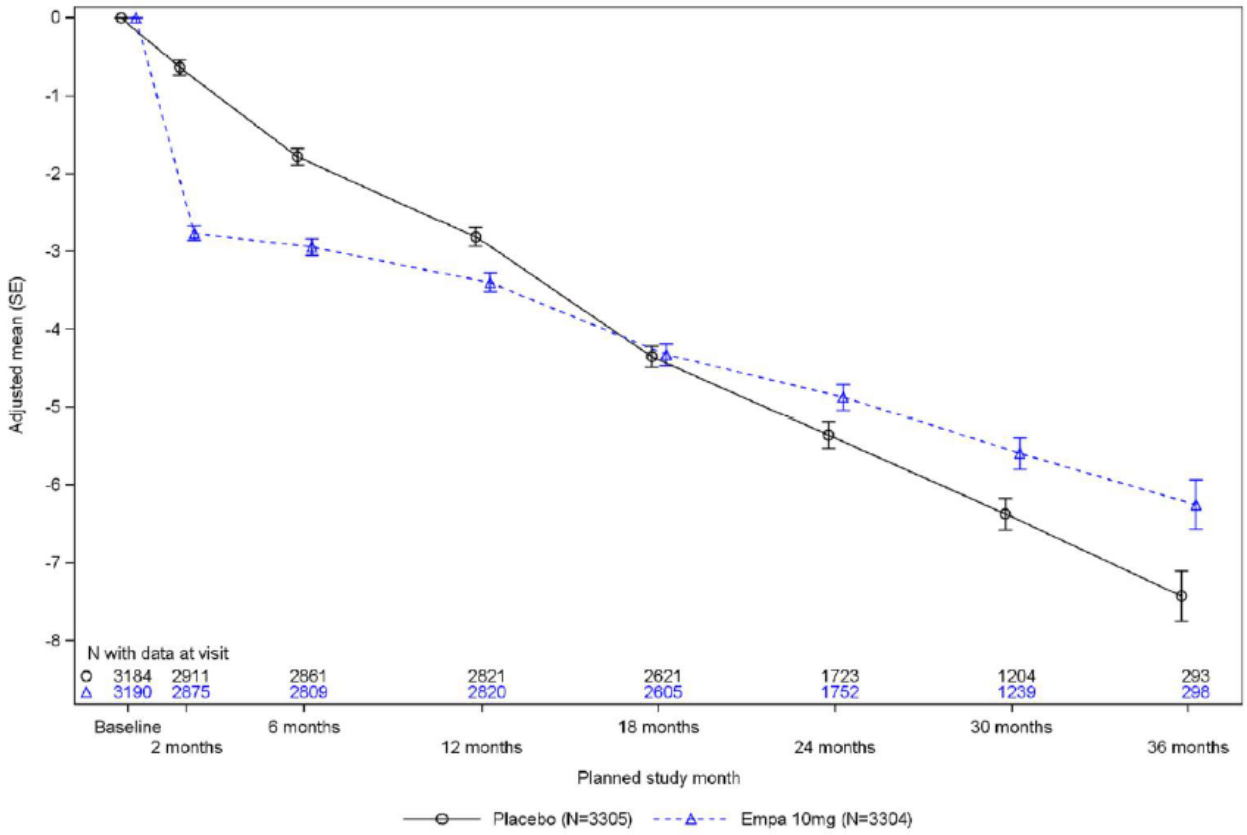
	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with ESKD, a sustained eGFR decline to <10 mL/min/1.73 m² or adjudicated renal death, N (%)	221 (6.7)	158 (4.8)
Incidence rate per 100 years at risk	3.47	2.47
Hazard ratio vs. placebo (95% CI)		0.69 (0.56, 0.85)
p-value		0.0004
Participants with a sustained eGFR decline ≥40%, N (%)	474 (14.3)	359 (10.9)
Incidence rate per 100 years at risk	7.58	5.67
Hazard ratio vs. placebo (95% CI)		0.70 (0.61, 0.81)
p-value		<0.0001
Participants with ESKD or adjudicated all-cause death, N (%)	299 (9.0)	245 (7.4)
Incidence rate per 100 years at risk	4.69	3.82
Hazard ratio vs. placebo (95% CI)		0.80 (0.67, 0.94)
p-value		0.0079
Participants with kidney disease progression or adjudicated all-cause death, N (%)	625 (18.9)	498 (15.1)
Incidence rate per 100 years at risk	10.03	7.90
Hazard ratio vs. placebo (95% CI)		0.75 (0.67, 0.84)
p-value		<0.0001
Participants with kidney disease progression or adjudicated CV death using cut-off of ≥50% eGFR decline, N (%)	388 (11.7)	279 (8.4)
Incidence rate per 100 years at risk	6.14	4.38
Hazard ratio vs. placebo (95% CI)		0.68 (0.58, 0.79)
p-value		<0.0001
Participants with kidney disease progression or adjudicated CV death using cut-off of ≥57% eGFR decline, N (%)	331 (10.0)	244 (7.4)
Incidence rate per 100 years at risk	5.22	3.82
Hazard ratio vs. placebo (95% CI)		0.71 (0.60, 0.83)
p-value		<0.0001
Participants with kidney disease progression using cut-off of ≥50% eGFR decline, N (%)	332 (10.0)	227 (6.9)
Incidence rate per 100 years at risk	5.25	3.56
Hazard ratio vs. placebo (95% CI)		0.64 (0.54, 0.76)
p-value		<0.0001
Participants with kidney disease progression using cut-off of ≥57% eGFR decline, N (%)	273 (8.3)	191 (5.8)
Incidence rate per 100 years at risk	4.31	2.99
Hazard ratio vs. placebo (95% CI)		0.67 (0.56, 0.81)
p-value		<0.0001
Participants with ESKD or a sustained decline in eGFR to <10 mL/min/1.73m², N (%)	221 (6.7)	157 (4.8)
Incidence rate per 100 years at risk	3.47	2.45
Hazard ratio vs. placebo (95% CI)		0.69 (0.56, 0.84)
p-value		0.0003
Participants with ESKD, N (%)	158 (4.8)	108 (3.3)
Incidence rate per 100 years at risk	2.48	1.68
Hazard ratio vs. placebo (95% CI)		0.67 (0.52, 0.85)
p-value		0.0012
Participants with a sustained decline in eGFR to <10 mL/min/1.73m², N (%)	167 (5.1)	116 (3.5)
Incidence rate per 100 years at risk	2.60	1.80
Hazard ratio vs. placebo (95% CI)		0.69 (0.54, 0.87)
p-value		0.0021

Cox regression model included factors age, sex, screening diabetes status, local screening eGFR, local screening UACR, region, and treatment.

- **eGFR changes over time (MMRM analyses)**

In the empagliflozin group, there was an initial drop in eGFR. The adjusted mean change from baseline (MMRM results) in eGFR [mL/min/1.73 m2] at 2 months in the empagliflozin group was -2.76 (95% CI -2.95, -2.58) and -0.64 (95% CI -0.82, -0.45) in the placebo group. After the initial drop, a slower decrease was observed for empagliflozin compared with placebo. This resulted in adjusted mean change from baseline at 36 months of -6.25 (95% CI -6.87, -5.63) in the empagliflozin group compared with -7.42 (95% CI -8.05, -6.79) in the placebo group. The treatment group difference in adjusted means for the average change from baseline over time was -0.31 (95% CI -0.60, -0.01).

Figure 3. eGFR [mL/min/1.73 m2] change from baseline over time, MMRM results (centrally assessed) – RS (OC-AD)



- **Annual rate of change in eGFR**

The annual rate of change in eGFR (allowing for the competing events of ESKD or death) was evaluated using a shared parameter model. The main analysis was based on central laboratory evaluations and included all samples collected prior to ESKD.

The total slope analysis was based on the time from baseline to final follow-up, therefore, the intercept reflects the modelled mean eGFR value per treatment group at baseline. As the analysis assumes a single linear relationship, the total slope results for the empagliflozin group are considered to be biased due to the non-linearity introduced by the acute drop in eGFR.

In contrast, the chronic slope analysis was performed based on the time from 2 months to final follow-up. The intercept in the chronic slope analysis reflects the mean change from baseline to the 2-month visit per group and can be interpreted as the acute slope of the initial 2 months. This acute slope was more pronounced in the empagliflozin group (-2.32 mL/min/1.73 m2) compared with the placebo group (-0.24 mL/min/1.73 m2). The annual rate of change from the 2-month visit onwards (i.e. the chronic slope) models

the approximately linear decline in the chronic phase. The chronic slope showed a greater eGFR decline in the placebo group compared with the empagliflozin group, with a between group difference of 1.37 mL/min/1.73 m2 per year (95% CI 1.16, 1.59) and relative difference to placebo of -50% (95% CI -56%, -44%).

Table 22. eGFR [mL/min/1.73 m2] annual rate of change, shared parameter model, allowing for events of ESKD or death – RS (OC-AD)

	Placebo	Empa 10 mg
Total slope (from baseline to final follow-up)		
Analysed participants, N	3305	3304
Intercept, estimate (95% CI)	37.30 (36.84, 37.75)	36.16 (35.70, 36.61)
Slope [/year], estimate (95% CI)	-2.92 (-3.07, -2.77)	-2.16 (-2.31, -2.01)
Difference vs. placebo (95% CI)		0.75 (0.54, 0.96)
p-value		<0.0001
Relative difference vs. placebo (95% CI) *		-0.26 (-0.32, -0.19)
p-value		<0.0001
Chronic slope (from 2 months to final follow-up)		
Analysed participants, N	3218	3219
Intercept, estimate (95% CI)	-0.24 (-0.42, -0.06)	-2.32 (-2.50, -2.14)
Slope [/year], estimate (95% CI)	-2.75 (-2.91, -2.59)	-1.37 (-1.53, -1.21)
Difference vs. placebo (95% CI)		1.37 (1.16, 1.59)
p-value		<0.0001
Relative difference vs. placebo (95% CI) *		-0.50 (-0.56, -0.44)
p-value		<0.0001

Model for total slope included factors age, sex, screening diabetes status, region, local screening UACR, region, treatment, treatment by time interaction.

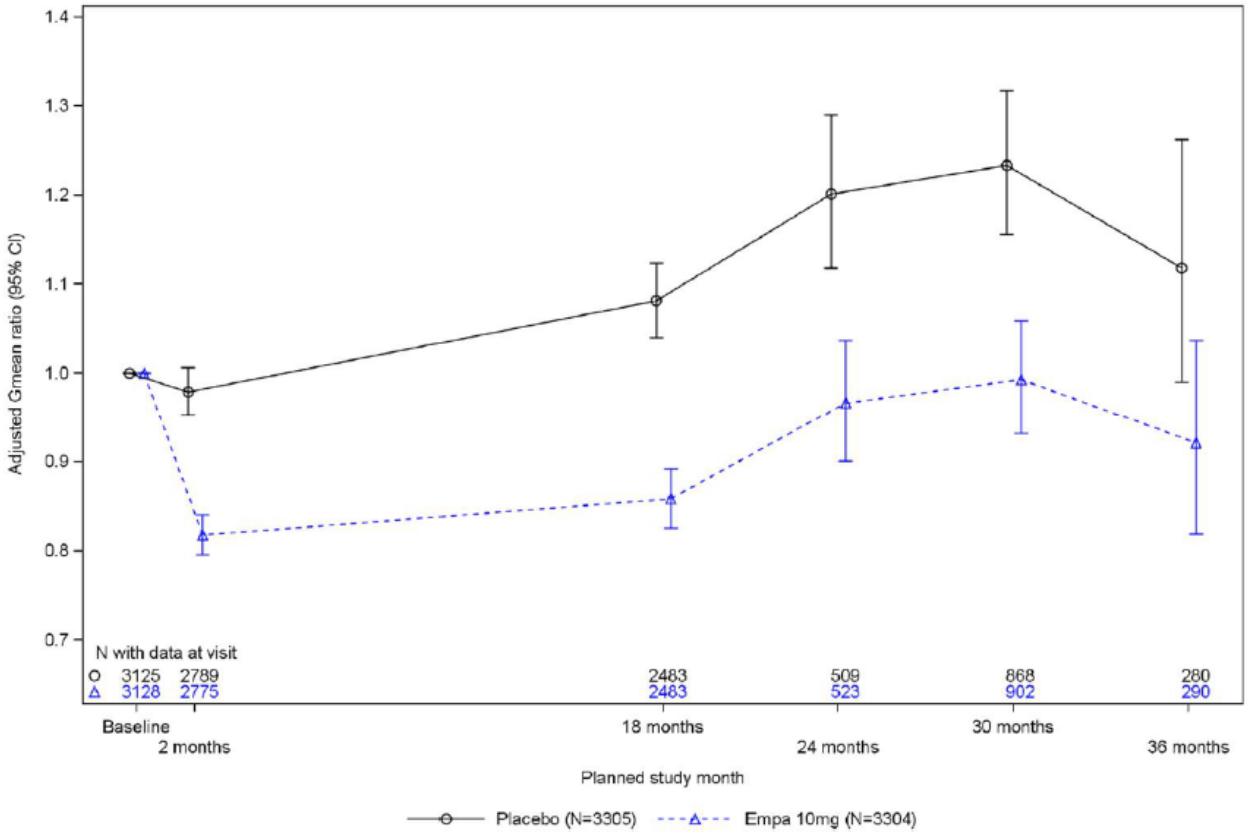
Model for chronic slope included factors baseline eGFR, baseline eGFR by time interaction, age, screening diabetes status, sex, local screening UACR, region, treatment, and treatment by time interaction.

*Relative differences (absolute difference as fraction of placebo slope) added as post-hoc summaries

- **UACR changes over time**

UACR initially decreased after 2 months in the empagliflozin group and later fluctuated below baseline, while UACR in the placebo group increased over the course of the trial (MMRM results). UACR remained lower in the empagliflozin group compared with the placebo group throughout the trial. The difference in the average relative change from baseline over time (MMRM results, gMean ratio) was 0.81 (95% CI 0.77, 0.85) for empagliflozin compared with placebo.

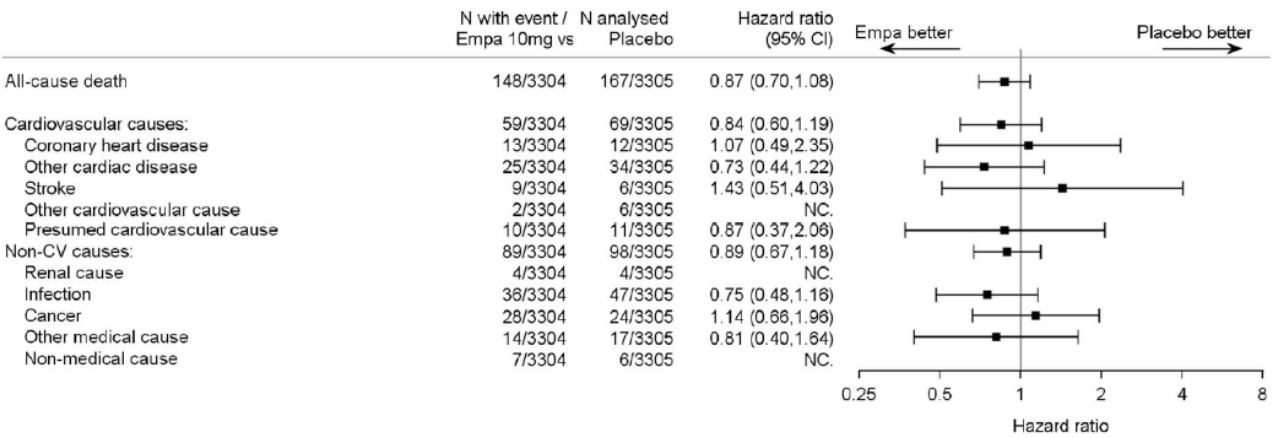
Figure 4. UACR (mg/g) relative change from baseline over time, MMRM results (centrally assessed) – RS (OC-AD)



- **Time to adjudicated death by category of cause**

Analyses of adjudicated death by different categories of cause did not indicate a treatment difference between the empagliflozin and placebo groups.

Figure 5. Forest plot of adjudicated causes of death – RS



- **Time to first occurrence of a major CV event**

The number of participants with an adjudicated major CV event (i.e. CV death, MI, stroke or HHF) was comparable between empagliflozin and placebo.

Table 23. Time to adjudicated major CV event, Cox regression – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with an adjudicated major CV event (CV death, MI, stroke or HHF), N (%)	213 (6.4)	200 (6.1)
Incidence rate per 100 years at risk	3.36	3.15
Hazard ratio vs. placebo (95% CI)		0.93 (0.76, 1.12)
p-value		0.4349

Cox regression model included factors age, sex, screening diabetes status, local screening eGFR, local screening UACR, region, and treatment.

- **Time to occurrence of adjudicated HHF**

The time to first occurrence of HHF (Cox regression) and a combined analysis of time to first and recurrent HHF (Joint frailty model) were analysed as further endpoints. There were no statistically significant treatment differences for either analysis of the time to occurrence of adjudicated HHF.

Table 24. Time to HHF – RS

	Placebo	Empa 10 mg
Analysed participants, N (%)	3305 (100.0)	3304 (100.0)
Participants with adjudicated HHF, first occurrence (Cox regression), N (%)	107 (3.2)	88 (2.7)
Incidence rate per 100 years at risk	1.67	1.37
Hazard ratio vs. placebo (95% CI) of adjudicated HHF		0.80 (0.60, 1.06)
p-value		0.1263
Total number of adjudicated HHF events, first and recurrent (Joint frailty model), N	154	118
Participants with adjudicated HHF then adjudicated death, N (%)	38 (1.1)	27 (0.8)
Participants with adjudicated HHF only, N (%)	69 (2.1)	61 (1.8)
Participants with adjudicated death only, N (%)	129 (3.9)	121 (3.7)
Hazard ratio vs. placebo (95% CI) of adjudicated HHF		0.78 (0.59, 1.04)
p-value		0.0922

Cox regression model included factors age, sex, screening diabetes status, local screening eGFR, local screening UACR, region, and treatment.

Joint frailty model (analysis of recurrent events accounting for terminal events) with terms for age, local screening UACR, local screening eGFR (CKD–EPI), treatment, sex, screening diabetes status, and region.

- **Time to new onset of diabetes**

The number of participants without diabetes at baseline who had new onset of diabetes during the trial was low in both treatment groups. There was no difference in the time to new onset of diabetes in participants without diabetes at baseline between the empagliflozin and placebo groups.

Table 25. Time to new onset of diabetes, Cox regression – RS

	Placebo	Empa 10 mg
Participants without diabetes at randomisation, N	1790	1779
Participants with new onset of diabetes, N (%)	61 (3.4)	51 (2.9)
Incidence rate per 100 years at risk	1.79	1.51
Hazard ratio vs. placebo (95% CI)		0.82 (0.56, 1.19)
p-value		0.2888
Participants without diabetes at randomisation with normoglycaemia (HbA_{1c} <39 mmol/mol), N	1254	1218
Participants with new onset of diabetes, N (%)	14 (1.1)	6 (0.5)
Incidence rate per 100 years at risk	0.59	0.26
Hazard ratio vs. placebo (95% CI)		0.43 (0.17, 1.13)
p-value		0.0869
Participants without diabetes at randomisation and prediabetic (HbA_{1c} ≥39 to <48 mmol/mol), N	536	561
Participants with new onset of diabetes, N (%)	47 (8.8)	45 (8.0)
Incidence rate per 100 years at risk	4.49	4.14
Hazard ratio vs. placebo (95% CI)		0.91 (0.60, 1.37)
p-value		0.6446

Cox regression model included factors age, sex, local screening eGFR, local screening UACR, region, and treatment.

- **Time to first occurrence of self-reported gout**

There was no difference in the time to first occurrence of self-reported gout between the empagliflozin and placebo groups: the event was reported by 278 participants (8.4%) in the empagliflozin group and 317 participants (9.6%) in the placebo group (HR 0.87, 95% CI 0.74, 1.02);

- **HbA1c changes over time**

The initial timepoints assessed for the majority of participants showed a greater reduction of HbA1c in the empagliflozin group compared with the placebo group, while the later timepoints considering fewer participants showed large variability. The average change from baseline over time (MMRM results) was -0.4 (95% CI -0.8, 0.0) for empagliflozin compared with placebo.

- **EQ-5D**

There were no relevant treatment differences in the descriptive analyses across the treatment groups in the scores of the EQ-5D questionnaire.

Ancillary analyses

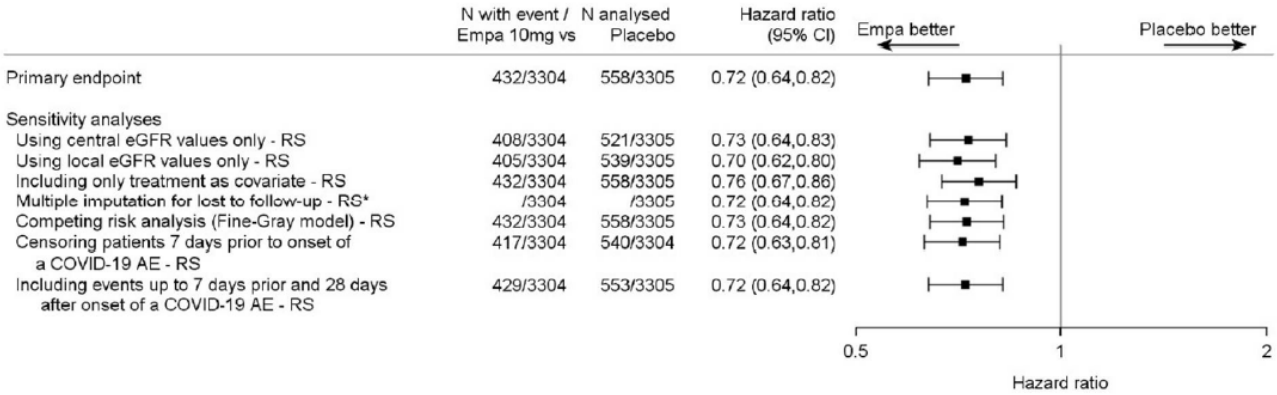
Sensitivity analyses of the primary endpoint

The cumulative probability for the censoring of participants without endpoint events were similar between treatment groups.

An exploratory analysis by year since randomisation was performed to explore whether the HR for the primary endpoint varied over time. The results were numerically similar and consistent with the overall results; HR (95% CI) was 0.73 (0.57, 0.94) in the first year, 0.68 (0.57, 0.82) in the second year, and 0.77 (0.61, 0.98) afterwards (trend test interaction p-value = 0.7241).

The sensitivity analyses were exploratory, and in all cases the results were consistent (i.e. the HR and CIs were similar) with the results of the primary analysis. There was no meaningful effect on the primary analysis results with respect to the presence of COVID-19 AEs.

Figure 6. Sensitivity analyses of the time to the first event of kidney disease progression or adjudicated CV death – RS



The tipping point analysis did not reveal any scenarios where the treatment effect in subjects with missing data would overturn the overall significant treatment effect obtained from the primary analysis. There were only 23 participants in the empagliflozin group and 18 in the placebo group, who were lost to follow-up with no evidence of a primary endpoint event, for whom data needed to be imputed.

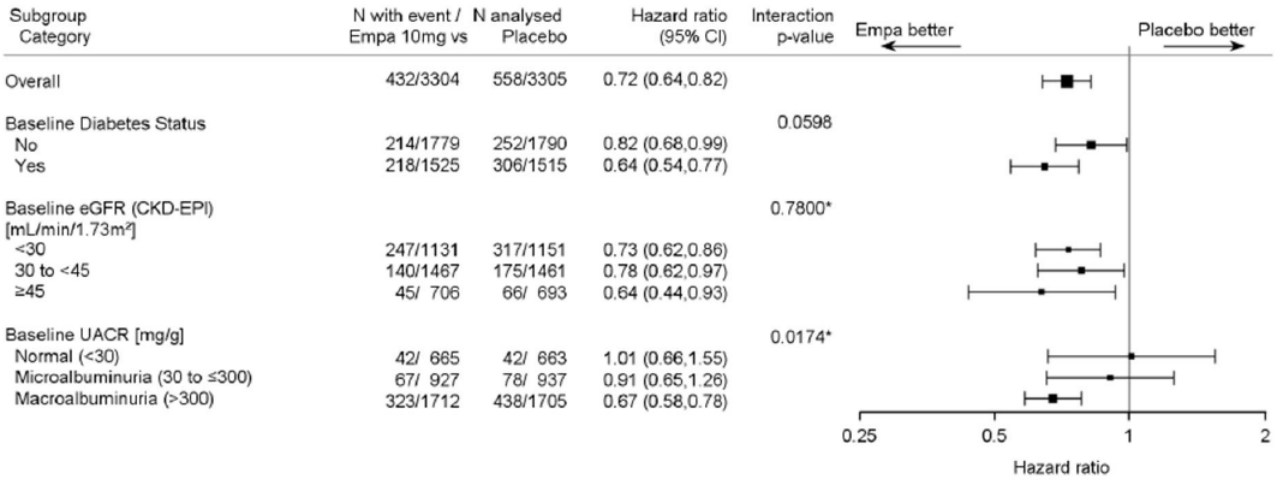
Subgroup analyses of the primary endpoint

Results of the *post hoc* sensitivity analysis based on the regions used in the randomisation minimisation process rather than the actual region (HR 0.73; 95% CI 0.64 to 0.82; p<0.0001; were consistent with the confirmatory analysis.

The results of the primary endpoint were consistent (interaction p-values >0.05) across the subgroups of key interest of baseline diabetes status and baseline eGFR, with the upper bound of the 95% CI for the HR for each subgroup <1.

There was a trend towards increasing treatment effect in participants with higher levels of UACR at baseline (trend test interaction p-value = 0.0174).

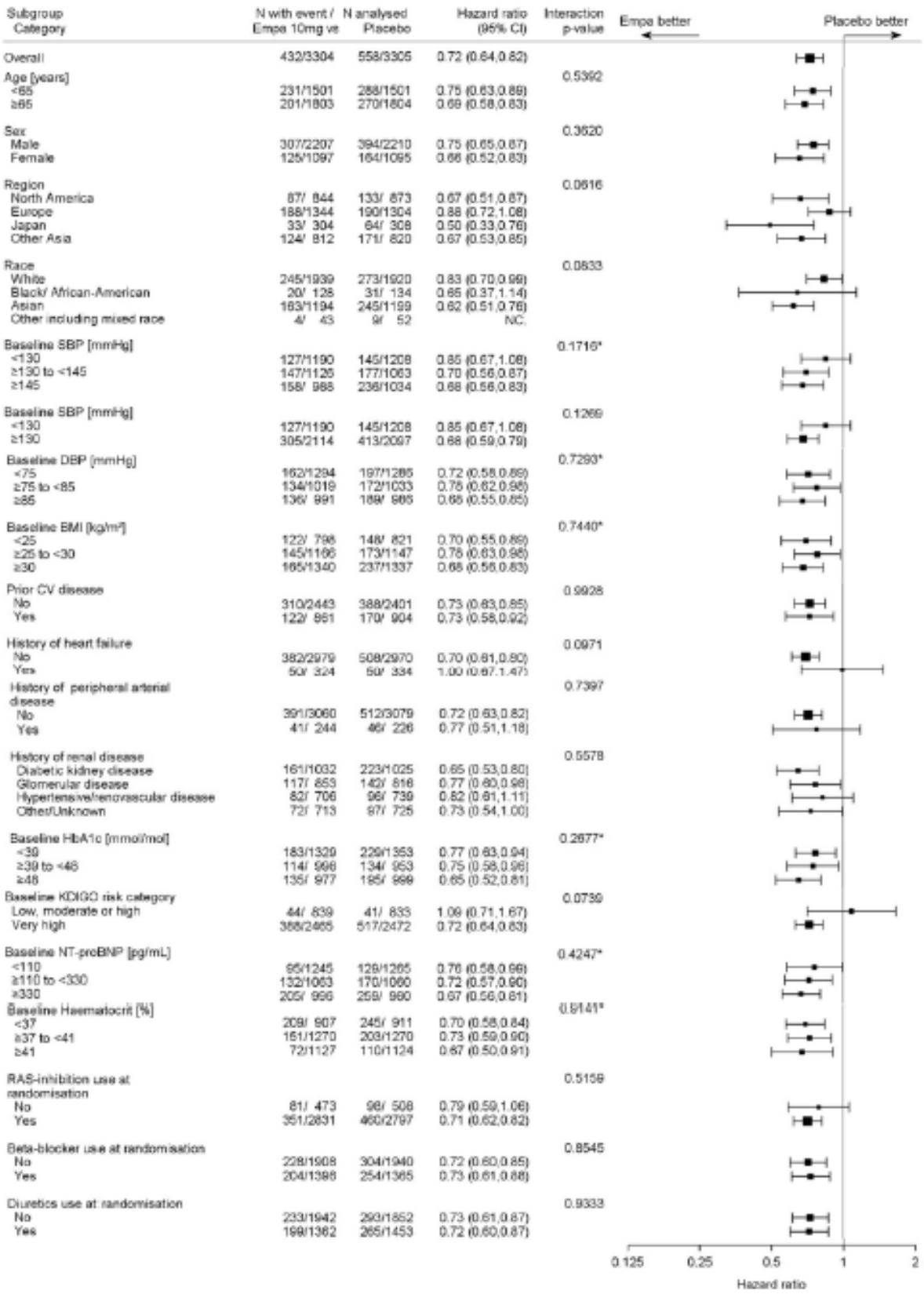
Figure 7. Key interest subgroup analyses of time to the first event of kidney disease progression or adjudicated CV death, Cox regression – RS



In the subgroup analysis by baseline eGFR <20, 20 to <30, 30 to <45, and ≥45 mL/min/1.73 m2, the results were consistent, HR (95% CI) was 0.73 (0.50, 1.06) for eGFR <20, 0.74 (0.61, 0.89) for eGFR 20 to <30, 0.78 (0.63, 0.98) for eGFR 30 to <45, and 0.64 (0.44, 0.93) for eGFR ≥45 mL/min/1.73 m2 (trend test interaction p-value = 0.8114).

In the subgroup analysis by baseline UACR <200 and ≥200 mg/g, the results were consistent: HR (95% CI) was 0.87 (0.66, 1.15) for UACR <200 mg/g and 0.71 (0.62, 0.82) for UACR ≥200 mg/g (interaction p-value = 0.2090).

Results of other subgroup analyses, including background use of RAS-inhibitors and underlying renal diseases, were consistent (interaction p-values >0.05); see figure below. Note that the subgroup analyses were not adjusted for multiple testing and effects observed in small subgroups are prone to random variation.



Summary of main study

The following table summarises the efficacy results from the main study supporting the present

application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26. Summary of Efficacy for trial

Title: A multicentre international randomised parallel group double-blind placebo-controlled clinical trial of Empagliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease			
Study identifier	**BI trial number:** 1245-0137/ **EudraCT number:** 2017-002971-24		
Design	Randomised, placebo-controlled, double-blind, parallel-group trial		
	Duration of main phase:		Event-driven until 1070 events (1 February 2019-5 July 2022), median 24.3 months
	Duration of Run-in phase:		8-12 weeks placebo run-in, appropriate background therapy including RAS inhibition
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Empagliflozin		Empagliflozin, 10 mg once daily, n=3304
	Placebo		Placebo, n=3305
Endpoints and definitions	Primary endpoint	Composite of renal disease progression or CV death	Time to first occurrence of kidney disease progression (defined as end stage kidney disease [ESKD], a sustained decline in eGFR to <10 mL/min/1.73 m2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomization*); or CV death ('as adjudicated')
	Secondary	Composite of HHF or CV death	Time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated')
	Secondary	All-cause Hospitalisations	Time to occurrences of all-cause hospitalisations (first and recurrent combined)
	Secondary	Death from any cause	Time to death from any cause ('as adjudicated')
Database lock	09 Sep 2022		

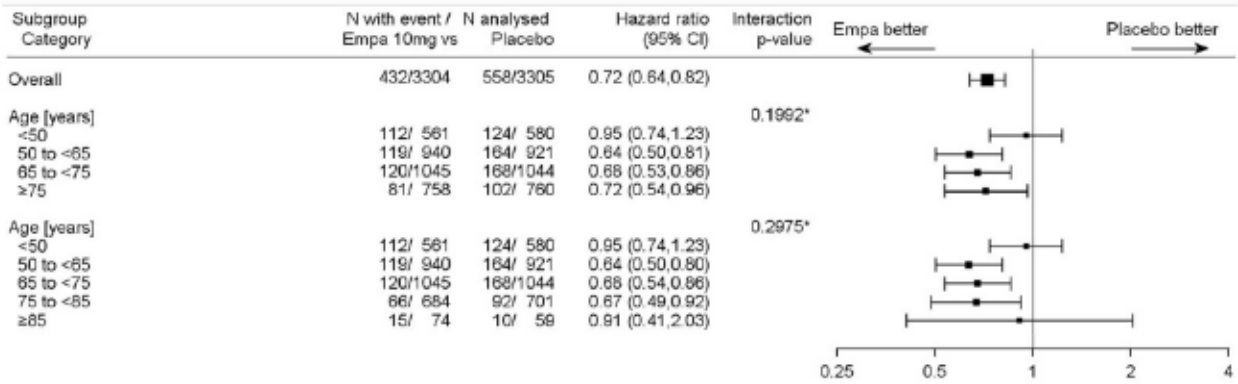
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Empagliflozin	Placebo
	Number of subjects	3304	3305
	Primary composite	432 (13.1%)	558 (16.9%)
	Secondary endpoint HHF or CV death	131 (4.0%)	152 (4.6%)
	Secondary endpoint all-cause hospitalisations	840 (25.4)	899 (27.2)
	Secondary endpoint All-cause death	148 (4.5)	167 (5.1)
Effect estimate per comparison	Primary endpoint	Comparison groups	Empagliflozin vs PLB
		HR	0.72
		95% CI	0.64, 0.82
		P-value	<0.0001
		Comparison groups	

	Secondary endpoint HHF or CV death	HR	0.84
		95% CI	0.67, 1.07
		P-value	0.153
	Secondary endpoint All-cause Hopitalisations	Comparison groups	
		HR	0.86
		95% CI	0.78, 0.95
		P-value	0.0025
	Secondary endpoint All-cause death	Comparison groups	
		HR	0.87
		95% CI	0.70, 1.08
		P-value	0.2137

Clinical studies in special populations

The table below presents the primary treatment effect of empaglifozin according to age levels <>65 years, > 75 years, > 85 years.

Figure 8. Subgroup analysis by age of time to first event of kidney disease progression or CV death, Cox regression – RS



Limited numbers of patients over 85 years of age were included in the study.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The EMPA-KIDNEY study was **designed** as a randomised, placebo-controlled, double-blind, parallel-group event-driven study to demonstrate superiority on slowing renal disease progression of empagliflozin 10 mg vs. placebo on top of guideline-directed medical therapy (including appropriate RASi background therapy) in a population generally at risk of kidney disease progression both with and without diabetes. The design of the study is generally acceptable to potentially demonstrate the defined objective.

The **key inclusion criteria** are patients with either eGFR ≥20 <45 mL/min/1.73m2, or an eGFR ≥45 – 90 mL/min/1.73m2 with urinary albumin/creatinine ratio ≥200 mg/g (or protein/creatinine ratio≥300 mg/g),

which can generally be considered a broad population at risk of further renal disease progression. However, a CKD population of patients with eGFR 45 to 60 (and 60 to 90) ml/min/1.73m2 without albuminuria was not included, likely due to a lower risk of disease progression. Furthermore, patients had to be on an appropriate dose of single agent RAS-inhibition with either ACEi or ARB, which appropriately reflects an important treatment element in the clinical care of these patients. Key exclusion criteria were maintenance dialysis, functioning kidney transplant, polycystic kidney disease and immunosuppressive usage (except prednisolone ≤10 mg or equivalent), which can be considered reasonable. Though the exclusion of patients with polycystic nephropathy and those receiving immunosuppressive medication does mean the trial is not fully representative of the whole CKD population, it is not considered needed to specifically mention this in the SmPC, comparable to other products of the same class (dapagliflozin).

The **primary endpoint** was a composite of time to the first occurrence of kidney disease progression (defined as end stage kidney disease [ESKD], a sustained decline in eGFR to <10 mL/min/1.73 m2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomisation); or CV death ('as adjudicated'), which is an acceptable composite and previously used in other renal studies to evaluate any potential protective renal treatment effect. All-cause mortality has been included as a **key secondary outcome** following hierarchical testing, which is acceptable and in line with SAWP recommendations. The key secondary endpoint of time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated') is mainly targeted at the evaluation of cardiovascular effects, which could be understood in the context of the known cardio-renal interaction in the disease targeted to be treated and further expand on the possible intercurrent effects. It has been explained by the Applicant that the key secondary endpoint of time to occurrences of all-cause hospitalisations (first and recurrent combined), may reflect the risk of disease burden and mortality. Further, a separation between renal and cardiovascular causes has been provided and shows consistent beneficial effects.

Other **secondary and exploratory endpoints,** including single endpoints of previously mentioned composite endpoints, other combinations of these endpoints, eGFR trajectories, and some adjudicated safety (gout) and biochemical endpoints (diabetes related), appear reasonable; however, they are not corrected for possible multiplicity, which limits their support for the main and key secondary findings.

Blinding methods are commonly used for such relatively large trials and can be considered acceptable. While the use of minimization allocation is not common for large studies, given the number of strata used, it can be understood and was agreed in the CHMP scientific advice. However, according to the same SAWP advice, re-randomisation tests were to be considered for the analysis of primary and secondary endpoints, given the fact that the random element used in the allocation is small (10%) and the primary analysis does not reflect the actual allocation procedure used. *Post-hoc* re-randomisation tests were performed, which showed consistency with the results of the primary analysis.

Other than the fact that the dynamic allocation was not reflected in the analyses, the analysis populations are acceptable, the analysis of the endpoints are considered standard and acceptable, and multiplicity across the endpoints is handled adequately.

Efficacy data and additional analyses

To include a sufficient number of patients, 8266 patients were screened in centres across the Globe, of which 1657 were not randomised. Of these, only 4.9% were not randomised due to valid reasons in accord with the inclusion and exclusion criteria of the study, while a large proportion was not randomised due to ineligible screening lab results. This latter description is rather vague, but was explained to be in relation to the eGFR and UACR values as eligibility criteria.

Of the 6609 patients randomised (3304 empagliflozin vs 3305 placebo), only 0.6% discontinued the trial, which is reassuring. A substantial number of 25.7% vs 22.9% discontinued study treatment, with 9.6% for

unknown reasons. Despite additional efforts by the Applicant, these reasons could not be retrieved. Further, this was only slightly increased for empagliflozin mainly due to reasons of adverse events (7.5% vs 7.1%), which may indicate that the study treatment was well tolerated during the study period.

In general, demographics were well-balanced between the treatment groups in the trial. The majority of subjects was elderly (55% > 65 years) and white male subjects (67%). Black or African American patients may be considered underrepresented (4.0%). A sufficient proportion of patients was included in Europe (40.1%). Following the inclusion criteria, patients had a mean eGFR of 37 mL/min/1.73 m2, with 52% having macro-albuminuria (>300 mg/g), representing a patient population at high risk of disease progression. The population was well stratified according to diabetes status, with 54% being non-diabetic. T1DM was an exclusion criterium, which seems reasonable based on the current indication, and only 1% with T1DM was included. The use of concomitant therapies was as expected, including RASi as cornerstone therapy (85%) in line with the treatment guidelines for CKD and was at baseline equally distributed between the treatment groups. More diuretics were administered during treatment for the placebo group (from 41.8% to 46.7% vs. 41.2% to 41.8%), which could implicitly support the renal benefits as observed (see below).

Empagliflozin showed a significantly superior effect for the primary endpoint of time to the first event of kidney disease progression or adjudicated CV death (432 (13.1%) vs 448 (16.9%); HR 0.72 (0.64, 0.82), p<0.001, which became evident after approximately 1 year of treatment. The primary endpoint was mainly driven by the eGFR reduction ≥40% surrogate (293 (8.9%) vs 373 (11.3%)), although every component demonstrated a lower number of events for empagliflozin during the study period. Consistency in all sensitivity analyses showed the robustness of the primary finding. Also, secondary and exploratory renal (composite) endpoints supported the major finding, including endpoints of time to first occurrence of kidney disease progression, time to different renal outcome definitions, a slower rate in eGFR change (slope), and slower annual rate for total slope and chronic slope. Further, the positive renal findings occurred before any CV effects emerged, with non-significant findings in overall mortality, CV mortality, CV endpoints (major CV events, time to HHF), and renal components driving the significance of any other combined renal/CV endpoints (time to CV death or ESKD). From a mechanistic point of view and as previously observed, the initial drop in eGFR and greater reduction in UACR with empagliflozin are of further support.

Although the renal findings appear convincing based on these findings and the sensitivity analyses, a slightly larger decrease in body-weight (-1.6 kg vs -0.7 kg already at month 6 and approximately -2.7 kg vs -1.7 kg at 36 months) was observed compared to placebo. However, this was not significantly different for muscle mass (rather body water) and is not believed to strongly alter the renal findings from a clinical perspective.

It could be questioned whether current data would sufficiently justify treatment across the full range of the CKD population as currently proposed in the extension of indication. The full range of the CKD population was not included in the study, but was limited to those with a eGFR 20 to 45 mL/min/1.73m2, or eGFR 45-90 mL/min/1.73m2 and albuminuria ≥200 mg/g. The possibility of extrapolation to patients possibly at lower risk of renal disease progression did not seem directly apparent from current trial. However, further evidence was provided by the Applicant during the procedure and following the assessment of all available data the CHMP considered it reasonable to accept the broader CKD indication. In support, the MAH provided and discussed data on the other studies previously submitted (EMPAREG-OUTCOME and EMPEROR studies) including patients with less advanced stages of CKD and moderate to high risk according to KDIGO criteria. These sufficiently large subgroups also show treatment benefits for patient with renal progression. In addition, a meta-analysis was submitted and discussed, showing efficacy combined and across several SGLT2i including patients for a range of mean eGFR baseline from 37 to 85 mL/min/1.73m2 m2 and a broad range of UACR. Also, from a mechanistic point of view, such data can be extrapolated to the current empagliflozin dossier. However, as for other SGLT2 inhibitors, data on an eGFR <20 ml/min/1.73m2 are

very limited and therefore initiation of empagliflozin in this lower eGFR range population is not supported. Section 4.2 (Posology and method of administration) of the SmPC was amended to reflect this information.

Further, although the primary results did appear to be consistent across the key subgroup of baseline eGFR, this appeared less consistent for diabetes status and albuminuria level. In non-diabetic patients, the effect was slightly less apparent (HR 0.82 (0.68, 0.99) vs diabetic (HR 0.64 (0.54, 0.77), although the p-value for interaction did not reach significance (0.0598). For albuminuria, a trend toward lower efficacy with lower albuminuria could be observed (p=0.0174), while no significant p for interaction was observed for urinary albumin:creatinine ratio < vs ≥200 mg/g (HR 0.87 (0.66, 1.15) and 0.71 (0.62, 0.82), respectively (interaction p-value = 0.2090)). In particular, in the normal to micro-albuminuria groups, a lack of or very limited efficacy appears to be present. A statement reflecting these findings is included in the SmPC. Presentation of patients in the lower KDIGO risk categories was limited, however, due to the additional discussion for the overall class and based on other studies with empagliflozin, not considered to be of major concern. A further presentation of data of treatment effects according to albuminuria subgroups and interaction with GFR subgroups and diabetes status are too limited to draw conclusions on, also because of inherent limitations of subgroups analyses.

A minor difference in reduction in HbA1c (-0.4 %) was observed. This may be expected, as the glucose-lowering effect of empagliflozin is eGFR dependent, thereby low in this population with reduced kidney function.

2.4.4. Conclusions on the clinical efficacy

In general, efficacy for a beneficial effect on renal disease progression of empagliflozin has been demonstrated, although it is not recommended to initiate treatment in a population with a eGFR < 20 ml/min/1.73m2, as reflected in the SmPC.

2.5. Clinical safety

Introduction

In the EMPA-KIDNEY trial, the collection of safety data was streamlined; only pre-specified non-serious AEs and SAEs were collected.

An exception was participants entered in Japanese sites, where all AEs (non-serious AEs and SAEs) were recorded. Unless stated otherwise the AE analyses detailed below were based on the pre-specified non-serious AEs and SAEs.

Safety analyses in the EMPA-KIDNEY trial followed the "treatment-emergent" principle and included all treated participants (TS). Unless otherwise specified, treatment was assigned as randomised and the analyses of AEs were based on the number of participants with AEs. AE analyses were restricted to "on-treatment" AEs, defined as AEs with an onset date between the first trial medication intake (i.e. randomisation) and 7 days after the last intake, unless otherwise stated. Exposure-adjusted AEs were also displayed as incidence rates per 100 patient years.

Patient exposure

Median observation time up to the end of the follow-up period was about 24 months in both treatment groups, with 98% of participants observed for at least 1 year and 51% for at least 2 years.

Table 27. Observational period up to the end of follow-up – RS

	Placebo	Empa 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Observation time categories, N (%)			
≥8 weeks	3302 (99.9)	3302 (99.9)	6604 (99.9)
≥26 weeks	3283 (99.3)	3283 (99.4)	6566 (99.3)
≥52 weeks	3240 (98.0)	3243 (98.2)	6483 (98.1)
≥78 weeks	2438 (73.8)	2422 (73.3)	4860 (73.5)
≥104 weeks	1674 (50.7)	1681 (50.9)	3355 (50.8)
≥130 weeks	710 (21.5)	728 (22.0)	1438 (21.8)
≥156 weeks	34 (1.0)	33 (1.0)	67 (1.0)
Observation time [months]			
Median (Q1, Q3)	24.33 (18.03, 29.70)	24.37 (18.00, 29.80)	24.33 (18.00, 29.73)
Mean (SD)	23.89 (6.94)	23.94 (6.95)	23.91 (6.95)
Total observation time [years]	6484.6	6495.4	12980.1

Observational time, used for majority of efficacy endpoints, was defined as time from randomisation to the date of the final follow-up visit

Median exposure to study medication was about 22 months in both treatment groups, with 91% of participants treated for at least 1 year and 44% for at least 2 years.

Table 28. Exposure to study medication – TS

	Placebo	Empa 10 mg	Total
Number of participants, N (%)	3305 (100.0)	3304 (100.0)	6609 (100.0)
Exposure categories, N (%)			
≥8 weeks	3274 (99.1)	3262 (98.7)	6536 (98.9)
≥26 weeks	3172 (96.0)	3161 (95.7)	6333 (95.8)
≥52 weeks	3007 (91.0)	3011 (91.1)	6018 (91.1)
≥78 weeks	2165 (65.5)	2170 (65.7)	4335 (65.6)
≥104 weeks	1444 (43.7)	1467 (44.4)	2911 (44.0)
≥130 weeks	590 (17.9)	606 (18.3)	1196 (18.1)
≥156 weeks	25 (0.8)	28 (0.8)	53 (0.8)
Duration of exposure [months]			
Median (Q1, Q3)	21.57 (16.73, 28.87)	21.92 (16.87, 28.93)	21.73 (16.80, 28.90)
Mean (SD)	22.06 (8.08)	22.15 (8.15)	22.10 (8.12)
Total exposure [years]	5987.3	6009.8	11997.1

Exposure time was defined as time from date of first intake until date of permanent discontinuation of study medication.

Adverse events

Overall safety profile

Empagliflozin and placebo groups had similar frequencies of participants with reported SAEs and prespecified non-serious AEs. The frequency of participants reported with AEs leading to discontinuation of study medication was also similar between the treatment groups. The frequency of participants with investigator-defined drug-related AEs was low. The frequency of participants with SAEs overall was comparable between groups. The frequency of participants with fatal AEs was similar in both groups.

Table 29. Overall summary of serious and prespecified non-serious adverse events – TS

Category of AEs	Placebo N (%)	Empa 10 mg N (%)
Number of participants	3305 (100.0)	3304 (100.0)
Participants with SAEs and prespecified non-serious AEs	1520 (46.0)	1447 (43.8)
Investigator-defined drug-related AEs	60 (1.8)	79 (2.4)
AEs leading to discontinuation of study medication	241 (7.3)	232 (7.0)
Participants with SAEs[1]	1167 (35.3)	1088 (32.9)
Results in death	93 (2.8)	88 (2.7)
Is life threatening	33 (1.0)	36 (1.1)
Persistent or significant disability/incapacity	17 (0.5)	14 (0.4)
Requires or prolongs hospitalisation	937 (28.4)	852 (25.8)
Congenital anomaly or birth defect	1 (<0.1)	0
Other medically important serious event[2]	315 (9.5)	308 (9.3)

Table 30. AEs by diabetes status – TS

Category of AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Without diabetes	1790 (100.0)		1779 (100.0)	
Any AE	698 (39.0)	28.02	667 (37.5)	26.41
Leading to discont. of study medication	84 (4.7)	2.59	97 (5.5)	3.01
SAEs	505 (28.2)	18.24	487 (27.4)	17.61
With diabetes	1515 (100.0)		1525 (100.0)	
Any AE	822 (54.3)	42.74	780 (51.1)	39.86
Leading to discont. of study medication	157 (10.4)	5.63	135 (8.9)	4.78
SAEs	662 (43.7)	30.15	601 (39.4)	26.68

Most frequently reported AEs

The frequencies of SAEs in each SOC were similar in the empagliflozin and placebo groups. The most frequently reported AEs were in the SOC metabolism and nutrition disorders, followed by infections and infestations, investigations, and renal and urinary disorders. The most frequently reported PTs were gout, acute kidney injury, and coronavirus infection. Additional serious and prespecified non-serious AEs with PTs reported in >2% of participants in either treatment group included blood potassium increased, dehydration, and hypoglycaemia.

Table 31. Participants with serious and prespecified non-serious adverse events (frequency >2% in either treatment group at the PT level) – TS

MedDRA SOC	Placebo		Empa 10 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Total with serious and prespecified non-serious AEs	1520 (46.0)	34.44	1447 (43.8)	32.28
Metabolism and nutrition disorders	445 (13.5)	8.06	416 (12.6)	7.51
Gout	266 (8.0)	4.66	231 (7.0)	4.02
Dehydration	65 (2.0)	1.09	72 (2.2)	1.20
Hypoglycaemia	67 (2.0)	1.12	68 (2.1)	1.13
Infections and infestations	324 (9.8)	5.60	355 (10.7)	6.17
Coronavirus infection	107 (3.2)	1.79	98 (3.0)	1.63
Investigations	199 (6.0)	3.39	177 (5.4)	3.00
Blood potassium increased	87 (2.6)	1.46	76 (2.3)	1.27
Renal and urinary disorders	182 (5.5)	3.06	158 (4.8)	2.65
Acute kidney injury	117 (3.5)	1.96	93 (2.8)	1.55

SAEs and protocol prespecified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.

Adverse events of special interest and specific adverse events

AESIs (adverse events of special interest) and specific AEs that represent medical concepts were analysed. To capture all events related to a specific medical concept, a combination of applicable adjudication results, investigator-defined events, standardised MedDRA query (SMQ), BI-customised MedDRA query (BIcMQ; when no SMQ was available), and/or additional definitions were used to analyse AESIs and specific AEs.

The overall frequencies for liver injury, serious urinary tract infection, serious genital infection, severe hypoglycaemia, and urinary tract malignancy were comparable in the empagliflozin and placebo groups. Ketoacidosis occurred in 6 participants in the empagliflozin group and 1 in the placebo group (0.10 and 0.02 per 100 participants-years, respectively). Lower limb amputations occurred in 26 participants in the empagliflozin group and 14 in the placebo group (0.43 and 0.23 per 100 participant-years, respectively). Within the individual categories of AESIs and specific AEs, generally similar proportions of participants in both treatment groups had serious AEs. Few AEs in any category of AESIs or specific AEs led to treatment discontinuation.

Table 32. Overall summary of AESIs and specific AEs – TS

Category of AESIs and specific AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Liver injury (adjudicated, AESI)	12 (0.4)	0.20	13 (0.4)	0.22
Serious	7 (0.2)	0.12	5 (0.2)	0.08
Up to 30 days after treatment discontinuation	12 (0.4)	0.20	13 (0.4)	0.22
Ketoacidosis (adjudicated, AESI)	1 (<0.1)	0.02	6 (0.2)	0.10
Serious	1 (<0.1)	0.02	6 (0.2)	0.10
Leading to discontinuation	0	0	0	0
Lower limb amputation (adjudicated, AESI)	14 (0.4)	0.23	26 (0.8)	0.43
Leading to discontinuation	1 (<0.1)	0.02	1 (<0.1)	0.02
Up to final follow up visit	19 (0.6)	0.29	28 (0.8)	0.43
Gout (user-defined)	303 (9.2)	5.35	270 (8.2)	4.75
Serious	7 (0.2)	0.12	8 (0.2)	0.13
Leading to discontinuation	0	0	1 (<0.1)	0.02
Serious hyperkalaemia (user-defined)	96 (2.9)	1.62	85 (2.6)	1.42
Leading to discontinuation	2 (0.1)	0.03	2 (0.1)	0.03
Serious urinary tract infection (narrow-sub BIcMQ)	47 (1.4)	0.78	42 (1.3)	0.70
Leading to discontinuation	5 (0.2)	0.08	3 (0.1)	0.05
Serious genital infection (adjudicated)	0	0	1 (<0.1)	0.02
Volume depletion (narrow sub-BIcMQ)	90 (2.7)	1.51	98 (3.0)	1.64
Hypotension (narrow sub-BIcMQ, subset of volume depletion)	22 (0.7)	0.36	22 (0.7)	0.36
Serious	41 (1.2)	0.68	46 (1.4)	0.76
Leading to discontinuation	1 (<0.1)	0.02	2 (0.1)	0.03
Symptomatic dehydration (user-defined)	70 (2.1)	1.17	80 (2.4)	1.34
Severe hypoglycaemic events (narrow SMQ)	72 (2.2)	1.21	74 (2.2)	1.24
Serious	14 (0.4)	0.23	13 (0.4)	0.21
Leading to discontinuation	2 (0.1)	0.03	1 (<0.1)	0.02
Bone fracture events (user-defined)	106 (3.2)	1.78	121 (3.7)	2.04
Serious	49 (1.5)	0.82	53 (1.6)	0.88
Leading to discontinuation	2 (0.1)	0.03	1 (<0.1)	0.02
Bone fracture events (narrow BIcMQ) up to trial completion	123 (3.7)	1.86	136 (4.1)	2.06
Urinary tract malignancy up to trial completion (broad sub-BIcMQ)	15 (0.5)	0.22	19 (0.6)	0.28

SAEs and protocol prespecified non-serious AEs included.
Adjudication of events stopped at final follow-up visit. The residual effect period afterwards was not considered.
SMQ, standardised MedDRA query; BIcMQ, Boehringer Ingelheim customised MedDRA query

- **Liver injury**

Similar frequencies were observed between groups for serious liver injury, and liver injury up to 30 days after treatment discontinuation. No relevant difference in the frequency of participants with liver injury was noted between treatment groups for subgroups by diabetes status.

Table 33. Participants with liver injury (AESI, adjudicated) – TS

MedDRA PT Cause of liver injury	Placebo N (%)	 Rate/100 pt-yrs	Empa 10 mg N (%)	 Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Liver injury (adjudicated)	12 (0.4)	0.20	13 (0.4)	0.22
Hepatitis	1 (<0.1)	0.02	6 (0.2)	0.10
Hepatitis toxic	4 (0.1)	0.07	1 (<0.1)	0.02
Hepatitis cholestatic	2 (0.1)	0.03	1 (<0.1)	0.02
Adenocarcinoma pancreas	0	0	1 (<0.1)	0.02
Alcohol abuse	0	0	1 (<0.1)	0.02
Coronavirus infection	1 (<0.1)	0.02	1 (<0.1)	0.02
Non−alcoholic fatty liver	1 (<0.1)	0.02	1 (<0.1)	0.02
Sepsis	0	0	1 (<0.1)	0.02
Biliary neoplasm	1 (<0.1)	0.02	0	0
Cardiac failure	1 (<0.1)	0.02	0	0
Influenza	1 (<0.1)	0.02	0	0
Liver injury (adjudicated), up to 30 days after treatment discontinuation	12 (0.4)	0.20	13 (0.4)	0.22
Liver injury (adjudicated), serious	7 (0.2)	0.12	5 (0.2)	0.08
Liver injury (adjudicated), serious, up to 30 days after treatment discontinuation	7 (0.2)	0.12	5 (0.2)	0.08
Fatal hepatobiliary disorder	2 (0.1)	0.03	5 (0.2)	0.08
With diabetes	7/1515 (0.5)	0.25	8/1525 (0.5)	0.29
Without diabetes	5/1790 (0.3)	0.16	5/1779 (0.3)	0.16

All serious and non-serious AEs of liver injury were collected [c37800399, Section 9.7.1.3.4].

Events confirmed or unrefuted by adjudication are considered as an endpoint event.

Residual effect period after final follow-up visit was not considered, as adjudication of events did not continue beyond the final follow-up visit.

See [c37800399, Section 15.4.3] for narratives for participants with fatal hepatobiliary disorders.

Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an adjudicated liver injury was 1.09 (95% CI 0.50, 2.38) (RS, OC-AD). The frequency of participants with elevated liver enzyme values was similar between treatment groups through the follow-up period including post-treatment events.

Table 34. Participants with elevated liver enzyme values – RS (OC-AD)

Elevated liver enzymes criteria	Placebo N (%)	Empa 10 mg N (%)	Risk ratio vs. placebo (95% CI)
Number of participants	3305 (100.0)	3304 (100.0)	
ALT or AST ≥5x ULN	12 (0.4)	13 (0.4)	1.08 (0.50, 2.37)
ALT or AST value ≥3x ULN with bilirubin ≥2x ULN	4 (0.1)	2 (0.1)	0.50 (0.09, 2.73)

Locally assessed liver transaminases collected at baseline, 2 month, 6-monthly and final follow-up visits. Bilirubin must be from the same blood sample as ALT or AST.

- **Ketoacidosis**

The rate of ketoacidosis (adjudicated) was low. The empagliflozin group had 6 participants with adjudicated events of ketoacidosis (narrow BIcMQ) overall, and by PTs including diabetic ketoacidosis and ketoacidosis, compared with one participant in the placebo group (0.10 vs. 0.02 per 100 patient-years, respectively).

Table 35. Participants with adverse events of ketoacidosis (AESI, adjudicated) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Ketoacidosis	1 (<0.1)	0.02	6 (0.2)	0.10
Diabetic ketoacidosis	1 (<0.1)	0.02	5 (0.2)	0.08
Ketoacidosis	0	0	1 (<0.1)	0.02
Ketoacidosis, serious	1 (<0.1)	0.02	6 (0.2)	0.10
Ketoacidosis, leading to discontinuation of study treatment	0	0	0	0
Male	1/2210 (<0.1)	0.02	3/2207 (0.1)	0.07
Female	0/1095 (0.0)	0	3/1097 (0.3)	0.15
With diabetes	1/1515 (0.1)	(0.04)	5/1525 (0.3)	0.18
Without diabetes	0/1790 (0.0)	0	1/1779 (0.1)	0.03

All serious and non-serious AEs of ketoacidosis were collected [c37800399, Section 9.7.1.3.4].
If adjudicated, the resulting preferred terms are presented.
Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

A nondiabetic female participant of 73 years in the empagliflozin group, had comorbidities such as left ventricular heart failure, ischemic heart disease and Stage IV CKD. After significant weight loss and poor oral intake for a few days prior, the participant presented with vomiting and dehydration and was diagnosed with AKI and ketoacidosis. Hospitalisation was required, study treatment was interrupted, and the participant recovered. The event was adjudicated as confirmed ketoacidosis.

The results regarding events of ketoacidosis analysed as specific AEs were the same as the results when analysed as AESIs, adjudicated.

Due to the small number of participants with events, the hazard ratio based on Cox regression for time to first occurrence of an adjudicated AESI of ketoacidosis was not calculated. The analysis of the estimated cumulative incidence of time to first occurrence of an adjudicated AESI of ketoacidosis showed the onset was within the first year for participants in the empagliflozin group.

- **Lower limb amputation**

Lower limb amputation (LLA) is summarised for EMPA-KIDNEY 1245-0137, and for a post-hoc meta-analysis of 4 large randomised, double-blind, placebo-controlled clinical outcome trials (EMPA-KIDNEY (1245-0137), EMPAREG-OUTCOME (1245-0025), EMPEROR-Preserved (1245-0110) and EMPEROR-Reduced (1245-0121),) (pooled dataset SAF-M3). The main focus should be the analyses including data through the final follow up because these include all events; results for the ontreatment period are also provided.

The frequency of participants with LLA (adjudicated) in the empagliflozin group and in the placebo group is provided in the table below. In both groups, the most commonly reported PT was toe amputation. The majority of events were reported in participants with diabetes.

Table 36. Participants with an AE of lower limb amputation (AESI, adjudicated) – TS, 1245-0137

MedDRA PT	Placebo		Empa 10 mg	
Level of amputation	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
LLA (adjudicated), up to 7 days after study treatment discontinuation	14 (0.4)	0.23	26 (0.8)	0.43
Toe amputation, toe or toes	13 (0.4)	0.22	18 (0.5)	0.30
Foot amputation, transmetatarsal	1 (<0.1)	0.02	5 (0.2)	0.08
Leg amputation	1 (<0.1)	0.02	7 (0.2)	0.12
Below knee	1 (<0.1)	0.02	5 (0.2)	0.08
Above knee	0	0	2 (0.1)	0.03
LLA (adjudicated), up to final follow-up visit	19 (0.6)	0.29	28 (0.8)	0.43
Toe amputation, toe or toes	14 (0.4)	0.22	20 (0.6)	0.31
Foot amputation, transmetatarsal	1 (<0.1)	0.02	7 (0.2)	0.11
Leg amputation	5 (0.2)	0.08	7 (0.2)	0.11
Below knee	4 (0.1)	0.06	5 (0.2)	0.08
Above knee	1 (<0.1)	0.02	2 (0.1)	0.03
LLA (adjudicated), among subgroups up to final follow-up visit				
Baseline eGFR <30 mL/min/1.73m²	10/1151 (0.9)	0.44	11/1131 (1.0)	0.49
Baseline eGFR 30 to <45 mL/min/1.73m²	6/1461 (0.4)	0.21	14/1467 (1.0)	0.49
Baseline eGFR ≥45 mL/min/1.73m²	3/693 (0.4)	0.23	3/706 (0.4)	0.22
Baseline UACR <30 mg/g	4/663 (0.6)	0.30	4/665 (0.6)	0.30
Baseline UACR 30 to ≤300 mg/g	6/937 (0.6)	0.33	10/927 (1.1)	0.55
Baseline UACR >300 mg/g	9/1705 (0.5)	0.27	14/1712 (0.8)	0.42
With diabetes	17/1515 (1.1)	0.56	23/1525 (1.5)	0.76
Without diabetes	2/1790 (0.1)	0.06	5/1779 (0.3)	0.15

All serious and non-serious AEs of LLA were collected [c37800399, Section 9.7.1.3.4].

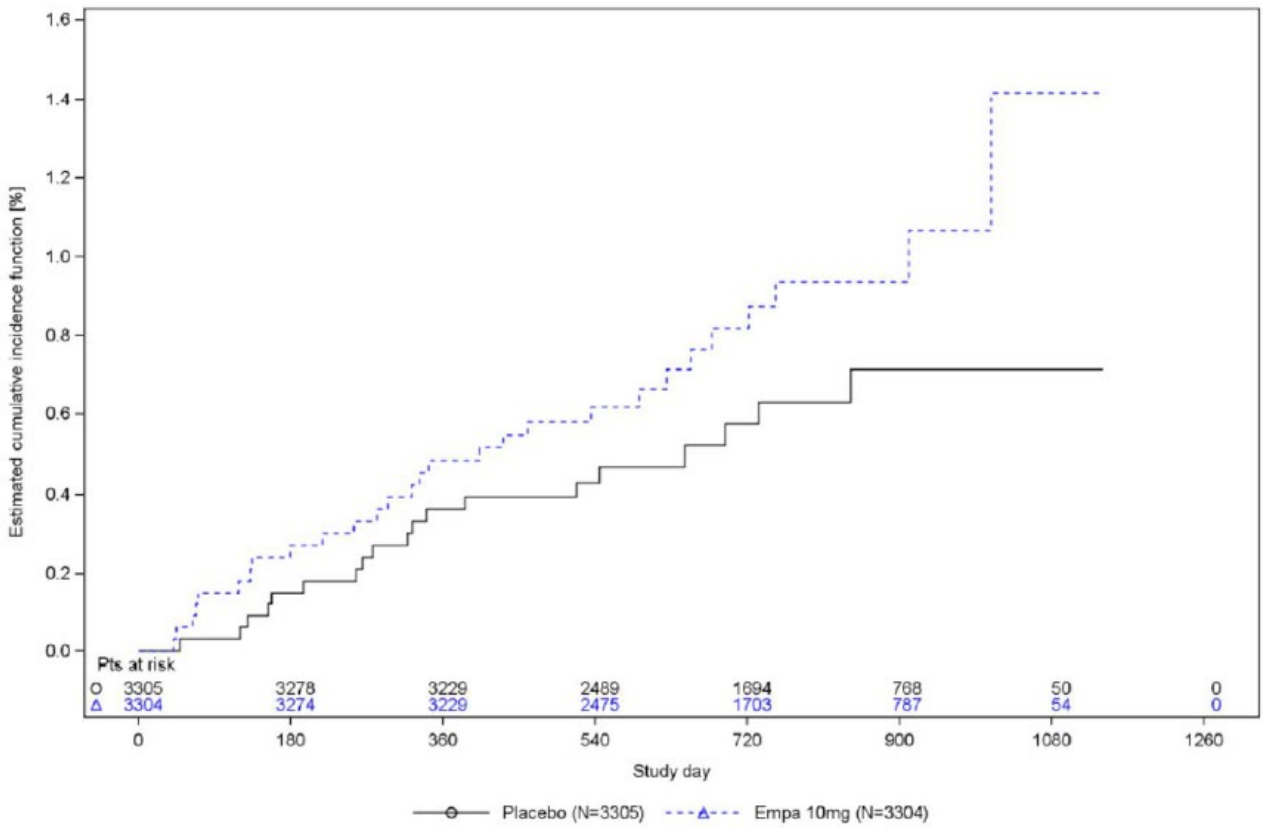
Events confirmed or unrefuted by adjudication are considered as an endpoint event.

LLA events selected from a user-defined list of preferred terms.

Residual effect period after final follow-up visit was not considered, as adjudication of events did not continue beyond the final follow-up visit.

In EMPA-KIDNEY, the hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an adjudicated LLA was 1.43 (95% CI 0.80, 2.57) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of LLA (adjudicated) in the empagliflozin and placebo groups started to diverge shortly after randomisation and remained separated throughout the trial.

Figure 9. Time to first occurrence of lower limb amputation (adjudicated) (user-defined) (all cause death as competing risk) – RS (OC–AD)



The *post-hoc* meta-analysis of trials EMPA-KIDNEY (1245-0137), EMPAREG-OUTCOME (1245-0025), EMPEROR-Preserved (1245-0110) and EMPEROR-Reduced (1245-0121), included 23,340 randomised and treated participants. The median duration of exposure to study drug was 1.93 years overall, 2.02 years in the all empagliflozin group, and 1.82 years in the placebo group. Total exposure was 25,823.7 patient-years in the all empagliflozin group and 19,526.3 patient-years in the placebo group. (The difference in exposure was due to the additional 25 mg empagliflozin treatment group in 1245-0025). The median observation period was 2.22 years in the empagliflozin group and 2.11 years in the placebo group.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of LLA during treatment was 1.16 (95% CI 0.86, 1.57); study treatment interaction p-value 0.34. The figure below shows the time to first LLA and the competing risk of time to all-cause mortality, whilst on-treatment. Considering events until the last follow-up, the hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of LLA was 1.05 (95% CI 0.81, 1.36); study treatment interaction p-value 0.38.

Figure 10. Estimated cumulative incidence function with death as a competing risk for time to first LLA on treatment – TS (SAF-M3)

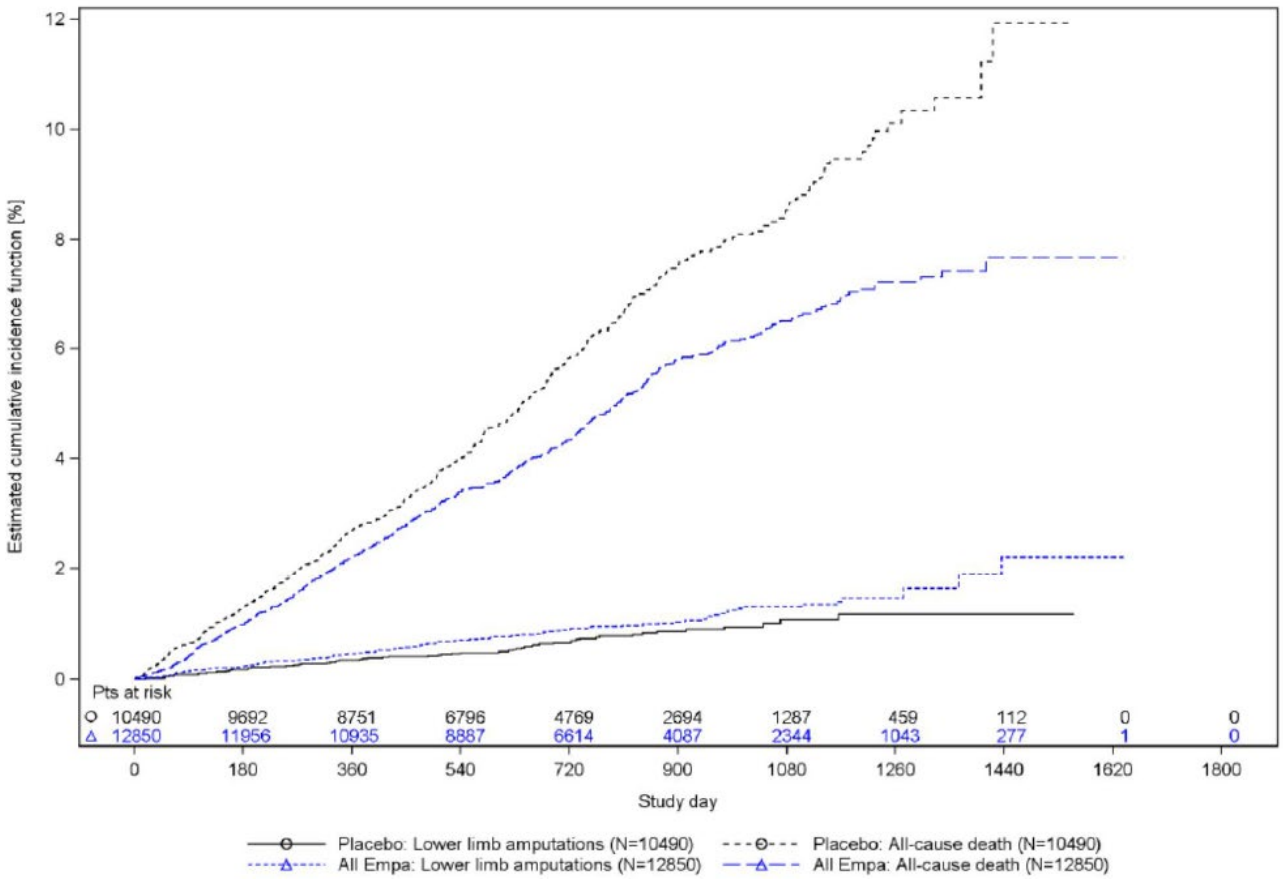


Figure 11. Forest plot of subgroup analyses of time to first LLA on treatment –TS, SAF-M3

Subgroup Category	N with event / All Empa vs	N analysed Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	121/12850	69/10490	1.16 (0.86,1.57)	
Baseline (eGFR) (CKD-EPI) [mL/min/1.73m²]				0.6544*
≥90	22/ 1782	9/ 1102	1.25 (0.57,2.71)	
60 to <90	38/ 4561	19/ 3401	1.12 (0.65,1.95)	
45 to <60	22/ 2371	17/ 2045	0.86 (0.45,1.62)	
30 to <45	25/ 2714	16/ 2534	1.29 (0.69,2.42)	
<30	14/ 1421	8/ 1405	1.63 (0.68,3.88)	
Baseline Diabetes Status				0.6858
Diabetic	115/ 8604	65/ 6245	1.14 (0.84,1.56)	
Non-Diabetic	6/ 4246	4/ 4245	1.49 (0.42,5.30)	
HF at baseline				0.1496
No	92/ 7205	40/ 5059	1.36 (0.93,1.98)	
Yes	29/ 5644	29/ 5430	0.85 (0.51,1.43)	

AEs potentially related to amputation, including cases not leading to amputation, were identified based on the list of PTs established by the EMA as an outcome of the Article 20 referral on LLA. The frequency of these event categories among participants in the 4 studies is shown in Table 36 through Table 40.

Table 37. Participants with vascular AEs –TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	99/2333 (4.2)	1.77	211/4687 (4.5)	1.81
1245-0110	67/2989 (2.2)	1.21	65/2996 (2.2)	1.17
1245-0121	32/1863 (1.7)	1.44	30/1863 (1.6)	1.33
1245-0137	48/3305 (1.5)	0.80	29/3304 (0.9)	0.48

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Table 38. Participants with diabetic foot related AEs – TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	43/2333 (1.8)	0.75	91/ 4687 (1.9)	0.76
1245-0110	21/2989 (0.7)	0.38	17/2996 (0.6)	0.30
1245-0121	4/1863 (0.2)	0.18	19/1863(1.0)	0.84
1245-0137	34/3305 (1.0)	0.57	50/3304 (1.5)	0.83

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Table 39. Participants with infections – TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	147/2333 (6.3)	2.64	257/4687 (5.5)	2.22
1245-0110	108/2989 (3.6)	1.97	97/2996 (3.2)	1.75
1245-0121	35/1863 (1.9)	1.57	42/1863 (2.3)	1.88
1245-0137	40/3305 (1.2)	0.67	51/3304 (1.5)	0.85

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Table 40. Participants with wound/infections – TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	64/2333 (2.7)	1.14	132/4687 (2.8)	1.12
1245-0110	34/2989 (1.1)	0.61	27/2996 (0.9)	0.48
1245-0121	17/1863 (0.9)	0.76	9/1863 (0.5)	0.40
1245-0137	28/3305 (0.8)	0.47	39/3304 (1.2)	0.65

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

Table 41. Participants with nervous system disorders – TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	139/2333 (6.0)	2.53	277/4687 (5.9)	2.41
1245-0110	51/2989 (1.7)	0.92	55/2996 (1.8)	0.99
1245-0121	15/1863 (0.8)	0.67	17/1863 (0.9)	0.75
1245-0137	121/3305 (3.7)	2.06	119/3304 (3.6)	2.01

Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

In Study EMPEROR-Reduced 1245.121, AEs related to diabetic foot were more frequently reported in the empagliflozin group. This is most probably a chance finding based on the very low frequency in the placebo group and the observation that, based on the KM analysis, no further event occurred on placebo after 1 year of treatment, which has no plausible medical explanation. Further, there is no plausible medical explanation why empagliflozin would increase the risk of diabetic foot-related AEs only in participants with HFrEF.

Table 42. Participants with AEs of volume depletion1 – TS

Trial	Placebo		Empagliflozin	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
1245-0025	16/2333 (0.7)	0.28	38/4687 (0.8)	0.32
1245-0110	50/2989 (1.7)	0.90	65/2996 (2.2)	1.16
1245-0121	24/1863 (1.3)	1.08	26/1863 (1.4)	1.16
1245-0137[2]	70/3305 (2.1)	1.17	80/3304 (2.4)	1.34

[1]Volume depletion includes the PTs dehydration and hypovolaemia, applicable to 1245-0025, 1245-0110, and 1245-0121.
[2]Symptomatic dehydration, applicable to 1245-0137.
Events up to first LLA included for 1245-0025, 1245-0110, and 1245-0121. All on-treatment events included for 1245-0137.

According to the MAH, no increased risk of LLA was seen in patients treated with empagliflozin. The data do not support that a common class-effect (e.g. dehydration) could explain the increased risk of LLA seen in the CANVAS studies with canagliflozin. No additional pharmacovigilance activities or additional risk minimisation measures are planned. In line with GVP Module V Rev 2, it is proposed:

- To demote this safety concern from the EU-RMP
- To further monitor this topic in the PBRER
- To no longer collect additional information about cases of LLA outside clinical trials with a dedicated questionnaire
- To consider LLA no longer as AESI in new studies, with the need to collect additional information about these events

- **Severe hypoglycaemia**

Similar frequencies of participants in both treatment groups were observed for SAEs of severe hypoglycaemia. Few participants in either group had severe hypoglycaemic events leading to treatment discontinuation.

Four non-diabetic participants in the empagliflozin group had severe hypoglycaemic events; one of the events was considered serious but not related to study treatment. In two cases, participants were taking concomitant traditional herbal mixes containing cinnamon, and in one case the participant was concomitantly on Valproic acid. All these medications are known to cause hypoglycemia. In the fourth case, the participant had concomitant gastric irritability and poor nutrition due to underlying H. pylori infection.

No relevant difference between treatment groups was observed for subgroups based on baseline eGFR category, or baseline UACR category.

The number and seriousness of hypoglycaemic episodes was similar between groups; few hypoglycaemic episodes led to permanent treatment discontinuation in either treatment group.

Table 43. Severe hypoglycaemic events (narrow SMQ, specific AEs) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Severe hypoglycaemic events (narrow SMQ)	72 (2.2)	1.21	74 (2.2)	1.24
Metabolism and nutrition disorders	67 (2.0)	1.12	68 (2.1)	1.13
Hypoglycaemia	67 (2.0)	1.12	68 (2.1)	1.13
Nervous system disorders	7 (0.2)	0.12	8 (0.2)	0.13
Hypoglycaemic unconsciousness	6 (0.2)	0.10	7 (0.2)	0.12
Hypoglycaemic coma	0	0	1 (<0.1)	0.02
Hypoglycaemic encephalopathy	1 (<0.1)	0.02	0	0
Severe hypoglycaemic events (narrow SMQ), serious	14 (0.4)	0.23	13 (0.4)	0.21
Severe hypoglycaemic events (narrow SMQ), leading to discontinuation of study treatment	2 (0.1)	0.3	1 (<0.1)	0.02
With diabetes	72/1515 (4.8)	2.65	70/1525 (4.6)	2.54
Without diabetes	0/1790 (0.0)	0	4/1779 (0.2)	0.12
Baseline eGFR <30 mL/min/1.73m²	35/1151 (3.0)	1.72	27/1131 (2.4)	1.32
Baseline eGFR 30 to <45 mL/min/1.73m²	32/1461 (2.2)	1.19	34/1467 (2.3)	1.28
Baseline eGFR ≥45 mL/min/1.73m²	5/693 (0.7)	0.40	13/706 (1.8)	1.01
Baseline UACR <30 mg/g	12/663 (1.8)	0.96	14/665 (2.1)	1.16
Baseline UACR 30 to ≤300 mg/g	26/937 (2.8)	1.54	22/927 (2.4)	1.31
Baseline UACR >300 mg/g	34/1705 (2.0)	1.12	38/1712 (2.2)	1.22
Episodes				
Number of hypoglycaemic episodes (episodes per 100 participant years)	110 (1.82)		90 (1.48)	
Number of serious hypoglycaemic episodes (episodes per 100 participant years)	15 (0.25)		13 (0.21)	
Number of hypoglycaemia episodes leading to permanent discont. of study treatment	2		1	

SAEs and protocol prespecified non-serious AEs included.

Severe hypoglycaemia events were prespecified as non-serious AEs to be collected [c37800399, Section 9.7.1.3.4].

Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

Baseline eGFR and UACR based on centrally assessed values (local values used if missing).

Severe hypoglycaemic episodes selected from a user-defined list of preferred terms.

- **Urinary tract infection**

The frequency of participants with an SAE of urinary tract infection (narrow sub-BIcMQ) between groups overall and by PT is provided in the table below. Few participants in either treatment group discontinued study treatment due to an SAE of urinary tract infection. No imbalances in the frequency of participants with an SAE of urinary tract infection were observed between treatment groups for subgroups based on sex or baseline diabetes status.

Table 44. Participants with serious urinary tract infection (specific AE, narrow sub-BIcMQ) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Serious urinary tract infection (narrow sub-BIcMQ)	47 (1.4)	0.78	42 (1.3)	0.70
Urinary tract infection	31 (0.9)	0.51	27 (0.8)	0.45
Urinary tract infection bacterial	6 (0.2)	0.10	7 (0.2)	0.12
Urosepsis	5 (0.2)	0.08	6 (0.2)	0.10
Pyelonephritis	3 (0.1)	0.05	3 (0.1)	0.05
Cystitis	1 (<0.1)	0.02	1 (<0.1)	0.02
Pyelonephritis acute	1 (<0.1)	0.02	1 (<0.1)	0.02
Renal abscess	1 (<0.1)	0.02	1 (<0.1)	0.02
Pyelocystitis	1 (<0.1)	0.02	0	0
Serious urinary tract infection (narrow sub-BIcMQ), leading to discontinuation of study treatment	5 (0.2)	0.08	3 (0.1)	0.05
Male	28/2210 (1.3)	0.70	25/2207 (1.1)	0.62
Female	19/1095 (1.7)	0.96	17/1097 (1.5)	0.85
With diabetes	28/1515 (1.8)	1.01	28/1525 (1.8)	0.99
Without diabetes	19/1790 (1.1)	0.59	14/1779 (0.8)	0.43

For subgroups, participants in subgroup with events/all participants in subgroup (%) are shown.

Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

Serious urosepsis (PT) or pyelonephritis (narrow sub BIcMQ) was reported for 10 participants in each treatment group. Serious urosepsis or pyelonephritis led to discontinuation of study treatment in none of the participants in the empagliflozin group and in four participants in the placebo group.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an SAE of urinary tract infection was 0.94 (95% CI 0.64, 1.37) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an SAE of urinary tract infection was the same between groups throughout the trial.

- **Genital infection**

There was one adjudicated SAE of genital infection in the trial through the treatment period and 7 days after (residual effect period); an SAE of fungal genital infection was reported for a female participant in the empagliflozin group who also had T2DM.

Through the final follow-up visit, one additional participant (male, in the placebo group) had an adjudicated SAE of genital infection. Due to just one participant per group with such an event, the hazard ratio based on Cox regression for time to first occurrence of an SAE of genital infection was not calculated (RS, OC-AD) and the analysis of the estimated cumulative incidence of time to first occurrence of an SAE of genital infection was not informative.

The analyses of serious genital infection (specific AE) (narrow sub-BIcMQ) were consistent with the adjudicated results, with no meaningful imbalances observed between groups overall (0.1%, empagliflozin; 0.1%, placebo).

- **Bone fracture**

The frequency of participants with an AE of bone fracture (specific AE) is provided in the table below.

Table 45. Participants with bone fracture (specific AE) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Bone fracture (user-defined)	106 (3.2)	1.78	121 (3.7)	2.04
Bone fracture (user-defined), serious	49 (1.5)	0.82	53 (1.6)	0.88
Bone fracture (user-defined), leading to discontinuation of study treatment	2 (0.1)	0.03	1 (<0.1)	0.02
Bone fracture (narrow BIcMQ), up to trial completion	123 (3.7)	1.86	136 (4.1)	2.06

Non-serious bone fracture AEs were prespecified to be collected [c37800399, Section 9.7.1.3.4].
Bone fracture events selected from a user-defined list of preferred terms.
Percentages calculated using total number of participants per treatment as the denominator.

Findings were similar when analysed as frequency of participants with bone fracture events (narrow BIcMQ) as these analyses included two additional participants in the empagliflozin group with events of bone fracture.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an AE of bone fracture was 1.08 (95% CI 0.84, 1.38) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an AE of bone fracture was similar between groups throughout the trial.

- **Urinary tract malignancy**

The frequencies of participants with urinary tract malignancies (broad sub-BIcMQs) up to trial completion were similar between treatment groups, with 19 participants (0.6%) in the empagliflozin group and 15 participants (0.5%) in the placebo group. The frequencies of participants with urinary tract malignancies ontreatment were also similar between treatment groups, with 18 participants (0.5%) in the empagliflozin group and 13 participants (0.4%) in the placebo group.

- **Volume depletion**

The frequency of participants with volume depletion (narrow sub-BIcMQ) compared with placebo is provided in the table below. In both treatment groups the most frequently reported PT was dehydration. The treatment groups were similar in the frequencies of participants with serious volume depletion and few participants in either group discontinued study treatment due to volume depletion. Subgroup analyses showed higher frequencies of volume depletion events among participants with diabetes, and those using RAS inhibitors or diuretics.

The frequency of participants with hypotension (narrow sub-BIcMQ) was similar between treatment groups. The treatment groups were balanced in the frequencies of participants with serious hypotension. One participant in each treatment group discontinued study treatment due to hypotension.

The frequency of participants with symptomatic dehydration between groups (symptomatic dehydration, user-defined) is provided in the table below. One participant in the empagliflozin group and no participants in the placebo group discontinued study treatment due to symptomatic dehydration.

Table 46. Participants with volume depletion (specific AE) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Volume depletion (narrow sub-BIcMQ)	90 (2.7)	1.51	98 (3.0)	1.64
dehydration	65 (2.0)	1.09	72 (2.2)	1.20
hypovolemia	5 (0.2)	0.08	8 (0.2)	0.13
syncope	8 (0.2)	0.13	16 (0.5)	0.26
presyncope	6 (0.2)	0.10	0	0
orthostatic hypotension	3 (0.1)	0.05	0	0
circulatory collapse	1 (<0.1)	0.02	1 (<0.1)	0.02
hypovolaemic shock	1 (<0.1)	0.02	1 (<0.1)	0.02
blood pressure decreased	4 (0.1)	0.07	4 (0.1)	0.07
Volume depletion (narrow sub-BIcMQ), serious	41 (1.2)	0.68	46 (1.4)	0.76
Volume depletion (narrow sub-BIcMQ), leading to discontinuation of study treatment	1 (<0.1)	0.02	2 (0.1)	0.03
With diabetes	46/1515 (3.0)	1.67	62/1525 (4.1)	2.24
Without diabetes	44/1790 (2.5)	1.37	36/1779 (2.0)	1.13
With RAS-inhibitor	69/2797 (2.5)	1.35	84/2831 (3.0)	1.63
Without RAS-inhibitor	21/508 (4.1)	2.47	14/473 (3.0)	1.75
With diuretics	50/1453 (3.4)	1.89	58/1362 (4.3)	2.33
Without diuretics	40/1852 (2.2)	1.21	40/1942 (2.1)	1.15
Hypotension (narrow sub-BIcMQ; part of volume depletion)	22 (0.7)	0.36	22 (0.7)	0.36
Hypotension (narrow sub-BIcMQ), serious	21 (0.6)	0.35	22 (0.7)	0.36
Hypotension (narrow sub-BIcMQ), leading to discontinuation of study treatment	1 (<0.1)	0.02	1 (<0.1)	0.02
Symptomatic dehydration (user-defined)	70 (2.1)	1.17	80 (2.4)	1.34
dehydration	65 (2.0)	1.09	72 (2.2)	1.20
hypovolemia	5 (0.2)	0.08	8 (0.2)	0.13
Symptomatic dehydration (user-defined), serious	21 (0.6)	0.35	26 (0.8)	0.43
Symptomatic dehydration (user-defined), leading to discontinuation of study treatment	0	0	1 (<0.1)	0.02

SAEs and prespecified non-serious AEs included.

Symptomatic dehydration events selected from a user-defined list of preferred terms.

Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

The hazard ratio based on Cox regression for empagliflozin participants vs. placebo for time to first occurrence of a (user-defined) dehydration SAE was 1.25 (95% CI 0.73, 2.14) (RS, OC-AD).

The hazard ratio based on Cox regression for empagliflozin participants vs. placebo for time to first occurrence of a symptomatic dehydration (user-defined) was 1.10 (95% CI 0.81, 1.51) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of a symptomatic dehydration (user-defined) in the empagliflozin and placebo groups started to diverge at randomisation but was similar after two years.

- **Acute kidney injury**

The frequency of participants with serious acute kidney injury (adjudicated) is provided in the table below. In both treatment groups, the most common cause of serious acute kidney injury was pre-renal haemodynamic. The stages of serious acute kidney injury were similar between treatment groups. The

frequency of participants with serious acute kidney injury was generally lower for participants in the empagliflozin group across subgroups.

Table 47. Participants with serious acute kidney injury (other adjudicated event) – TS

	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Participants with serious acute kidney injury (adjudicated)	117 (3.5)	1.97	93 (2.8)	1.56
Cause				
Pre-renal haemodynamic	58 (1.8)	0.97	46 (1.4)	0.77
Hypovolaemia	18 (0.5)	0.30	22 (0.7)	0.37
Unknown	21 (0.6)	0.35	15 (0.5)	0.25
Nephrotoxic medication	12 (0.4)	0.20	4 (0.1)	0.07
Obstructive	3 (0.1)	0.05	9 (0.3)	0.15
Intrinsic renal disease	9 (0.3)	0.15	1 (<0.01)	0.02
Stage				
Stage 1 (≥1.5 to <2x historical value[s])	49 (1.5)	0.82	47 (1.4)	0.79
Stage 2 (≥2 to <3x historical value[s])	28 (0.8)	0.47	26 (0.8)	0.43
Stage 3 (≥3x historical value[s] or renal replacement therapy initiation)	45 (1.4)	0.75	23 (0.7)	0.38
Unknown stage	1 (<0.1)	0.02	1 (<0.1)	0.02
Baseline eGFR <30 mL/min/1.73m²	54/1151 (4.7)	2.66	53/1131 (4.7)	2.63
Baseline eGFR 30 to <45 mL/min/1.73m²	50/1461 (3.4)	1.87	35/1467 (2.4)	1.32
Baseline eGFR ≥45 mL/min/1.73m²	13/693 (1.9)	1.05	5/706 (0.7)	0.39
Baseline UACR <30 mg/g	15/663 (2.3)	1.21	14/665 (2.1)	1.17
Baseline UACR 30 to ≤300 mg/g	33/937 (3.5)	1.96	32/927 (3.5)	1.92
Baseline UACR >300 mg/g	69/1705 (4.0)	2.30	47/1712 (2.7)	1.52
With diabetes	73/1515 (4.8)	2.66	65/1525 (4.3)	2.35
Without diabetes	44/1790 (2.5)	1.38	28/1779 (1.6)	0.88
With RAS-inhibitor	94/2797 (3.4)	1.85	78/2831 (2.8)	1.51
Without RAS-inhibitor	23/508 (4.5)	2.71	15/473 (3.2)	1.90
With diuretics at randomisation	78/1453 (5.4)	2.96	54/1362 (4.0)	2.17
Without diuretics at randomisation	39/1852 (2.1)	1.18	39/1942 (2.0)	1.13

Events confirmed or unrefuted by adjudication are considered as an endpoint event.

Acute kidney injury events selected from a user-defined list of preferred terms.

Residual effect period after final follow-up visit was not considered as adjudication of events did not continue beyond the final follow-up visit.

Stage adapted from 2012 KDIGO guidance and based on serum creatinine increases.

Baseline eGFR and UACR based on centrally assessed values (local values used if missing).

Baseline diabetes from reported history, diabetes-related AE, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol.

Results were the same for the analyses of participants with serious acute kidney injury (specific AE).

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an SAE of acute kidney injury (adjudicated) was 0.78 (95% CI 0.60, 1.00) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an SAE of kidney injury (adjudicated) in the empagliflozin and placebo groups started to diverge shortly before one year after randomisation and remained separated throughout the trial.

- **Gout**

The frequency of participants with gout, SAE(s) of gout, and gout leading to discontinuation of study treatment is provided in the table below

Table 48. Participants with gout – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Gout (user-defined) [1]	303 (9.2)	5.35	270 (8.2)	4.75
Gout (user-defined), serious	7 (0.2)	0.12	8 (0.2)	0.13
Gout (user-defined), leading to discontinuation of trial treatment[1]	0	0	1 (<0.1)	0.02

Gout events selected from a user-defined list of preferred terms.

Serious and non-serious gout AEs were prespecified to be collected [c37800399, Section 9.7.1.3.4].

- **Hyperkalaemia**

The frequency of participants with serious hyperkalaemia is provided in the table below.

Hyperkalaemia leading to discontinuation of study medication was reported for two participants in each treatment group.

Table 49. Participants with serious hyperkalaemia – TS

SOC/MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Serious hyperkalaemia (user-defined)	96 (2.9)	1.62	85 (2.6)	1.42
Investigations				
Blood potassium increased	87 (2.6)	1.46	76 (2.3)	1.27
Metabolic and nutrition disorders				
Hyperkalaemia	14 (0.4)	0.23	14 (0.4)	0.23
Hyperkalaemia (user-defined), leading to discontinuation from trial medication	2 (0.1)	0.03	2 (0.1)	0.03

Hyperkalaemia events selected from a user-defined list of preferred terms.

The hazard ratio based on Cox regression for empagliflozin vs. placebo for time to first occurrence of an SAE of hyperkalaemia was 0.83 (95% CI 0.63, 1.09) (RS, OC-AD). The estimated cumulative incidence of time to first occurrence of an SAE of hyperkalaemia started to diverge at randomisation and remained separated throughout the trial.

Potassium (mmol/L) change from baseline over time MMRM results showed the treatment groups diverged shortly after randomisation and remained separated throughout the trial.

Serious adverse event/deaths/other significant events

The overall frequency of participants with SAEs was comparable between treatment groups. SAEs were most frequently reported in the SOCs renal and urinary disorders, and in infections and infestations. The most common PTs were acute kidney injury and coronavirus infection. The most commonly reported SAEs (PTs reported in >1% of participants in either group) are summarised in the table below. No relevant difference between treatment groups was observed in the frequency of participants with SAEs assessed by the investigator as drug-related.

Table 50. Participants with SAEs (frequency >1% in either treatment group at the PT level) – TS

MedDRA SOC	Placebo		Empa 10 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Total with SAEs	1167 (35.3)	23.51	1088 (32.9)	21.68
Renal and urinary disorders	177 (5.4)	2.98	157 (4.8)	2.63
Acute kidney injury	117 (3.5)	1.96	93 (2.8)	1.55
End stage renal disease	27 (0.8)	0.45	35 (1.1)	0.58
Infections and infestations	297 (9.0)	5.11	296 (9.0)	5.09
Coronavirus infection	107 (3.2)	1.79	98 (3.0)	1.63
Pneumonia	42 (1.3)	0.70	39 (1.2)	0.65
Investigations	190 (5.7)	3.23	168 (5.1)	2.85
Blood potassium increased	87 (2.6)	1.46	76 (2.3)	1.27
Blood creatinine increased	56 (1.7)	0.93	43 (1.3)	0.71
Cardiac disorders	203 (6.1)	3.45	179 (5.4)	3.02
Ischaemic cardiomyopathy	45 (1.4)	0.75	33 (1.0)	0.55
Cardiac failure	44 (1.3)	0.73	41 (1.2)	0.68
Myocardial infarction	31 (0.9)	0.51	39 (1.2)	0.65
Atrial fibrillation	32 (1.0)	0.53	18 (0.5)	0.30
Nervous system disorders	108 (3.3)	1.81	101 (3.1)	1.69
Ischaemic stroke	34 (1.0)	0.56	30 (0.9)	0.50
With investigator-defined drug-related SAEs	11 (0.3)	0.18	16 (0.5)	0.26

If adjudicated, the resulting preferred terms are presented.

Deaths

Fatal AEs on treatment were reported for 3.8% of participants in the empagliflozin group (event rate 2.09 per 100 participant years) and 4.1% of participants in the placebo group (event rate 2.25 per 100 participant years). Fatal AEs up to the final follow-up visit were reported for 4.5% of participants in the empagliflozin group (event rate 2.28 per 100 participant years) and 5.1% of participants in the placebo group (event rate 2.61 per 100 participant years).

Table 51. Participants with fatal AEs by protocol-specified categorisation – TS

Main death category Sub-category	Placebo N (%)	Empa 10 mg N (%)
Number of participants	3305 (100.0)	3304 (100.0)
Participants with fatal AEs (adjudicated)	135 (4.1)	126 (3.8)
Cardiovascular cause	60 (1.8)	52 (1.6)
Coronary heart disease	10 (0.3)	11 (0.3)
Other cardiac disease	30 (0.9)	20 (0.6)
Stroke	6 (0.2)	9 (0.3)
Other cardiovascular	5 (0.2)	2 (0.1)
Presumed cardiovascular	9 (0.3)	10 (0.3)
Non-cardiovascular cause	75 (2.3)	74 (2.2)
Renal	3 (0.1)	3 (0.1)
Infection	39 (1.2)	35 (1.1)
Cancer	18 (0.5)	21 (0.6)
Other medical	11 (0.3)	12 (0.4)
Non-medical	4 (0.1)	3 (0.1)
Participants with fatal AEs (adjudicated), up to final follow-up visit	169 (5.1)	148 (4.5)

Laboratory findings

Clinical laboratory values measured within 3 days after discontinuation of study medication were considered as 'on-treatment'.

Elevations in local laboratory measures of ALT and AST as trial-specific safety endpoints are summarised together with liver injury AEs. Results of potassium at each scheduled visit during the follow-up as a trial-specific safety endpoint are summarised together with hyperkalaemia AEs.

This section summarises the results of haematocrit, haemoglobin, sodium, corrected calcium and phosphate at 18 months in the subset of UK participants (trial-specific safety endpoint) as well as the standard analyses of laboratory parameters. Changes from baseline to 18 months in haematocrit and haemoglobin were compared between the treatments using ANCOVA with baseline fitted as a covariate. Mean values at 18 months for sodium, corrected calcium, and phosphate were compared between the treatments using t-tests, as baseline assessments were not taken.

Haematology

Haemoglobin and haematocrit levels at Month 18 were higher in the empagliflozin group than the placebo group in UK participants. Both parameters showed an increase compared with baseline in the empagliflozin group and a decrease in the placebo group (see table below). The percentage of UK participants with 'possibly clinically significant abnormalities' for high values was 1.8% in the empagliflozin group and 0.5% in the placebo group for haemoglobin and 1.3% in the empagliflozin group and 0.5% in the placebo group for haematocrit.

Table 52. ANCOVA results for haemoglobin and haematocrit, locally assessed (UK participants only) – RS (OC-AD)

	Placebo	Empa 10 mg
Haemoglobin [g/dL]		
Analysed participants, N	374	437
Baseline, mean (SE)	12.95 (0.09)	12.90 (0.08)
Value at Month 18, adjusted[1] mean (95% CI)	12.79 (12.67, 12.90)	13.53 (13.42, 13.64)
Change from baseline	-0.14 (-0.26, -0.02)	0.60 (0.49, 0.71)
Comparison vs. placebo		0.74 (0.58, 0.90)
Haematocrit [%]		
Analysed participants, N	300	347
Baseline, mean (SE)	38.92 (0.29)	38.74 (0.26)
Value at Month 18, adjusted[1] mean (95% CI)	38.24 (37.82, 38.66)	40.62 (40.23, 41.01)
Change from baseline	-0.58 (-1.00, -0.16)	1.80 (1.41, 2.19)
Comparison vs. placebo		2.38 (1.81, 2.95)

[1] Model for 18 months includes baseline value as linear covariates and treatment as fixed effects.

Other parameters

Mean ALT at the last value on treatment was 22.3 U/L in the empagliflozin group and 21.6 U/L in the placebo group. Mean AST at the last value on treatment was 25.8 U/L in the empagliflozin group and 24.0 U/L in the placebo group. Similar percentages of participants in both treatment groups had shifts from a normal value at baseline to a value below or above normal at the last value on treatment for ALT, AST, alkaline phosphatase, and total bilirubin (data not shown). The analysis of ALT and AST elevations by categories is presented as part of the assessment of liver injury.

Mean values for sodium, corrected calcium, and phosphate at Month 18 for UK participants are presented in the table below.

Table 53. t-test results for sodium, corrected calcium and phosphate, locally assessed (UK participants only) – RS (OC-AD)

	Placebo	Empa 10 mg
Sodium [mmol/L]		
Analysed participants, N	395	442
Value at Month 18, adjusted[2] mean (95% CI)	138.8 (138.6, 139.1)	139.3 (139.0, 139.5)
Comparison vs. placebo		0.4 (0.1, 0.8)
Corrected calcium [mmol/L]		
Analysed participants, N	326	380
Value at Month 18, adjusted[1] mean (95% CI)	2.3533 (2.3405, 2.3661)	2.3617 (2.3499, 2.3735)
Comparison vs. placebo		0.0084 (-0.0090, 0.0258)
Phosphate [mmol/L]		
Analysed participants, N	313	380
Value at Month 18, adjusted[1] mean (95% CI)	1.138 (1.109, 1.167)	1.171 (1.145, 1.198)
Comparison vs. placebo		0.034 (-0.006, 0.073)

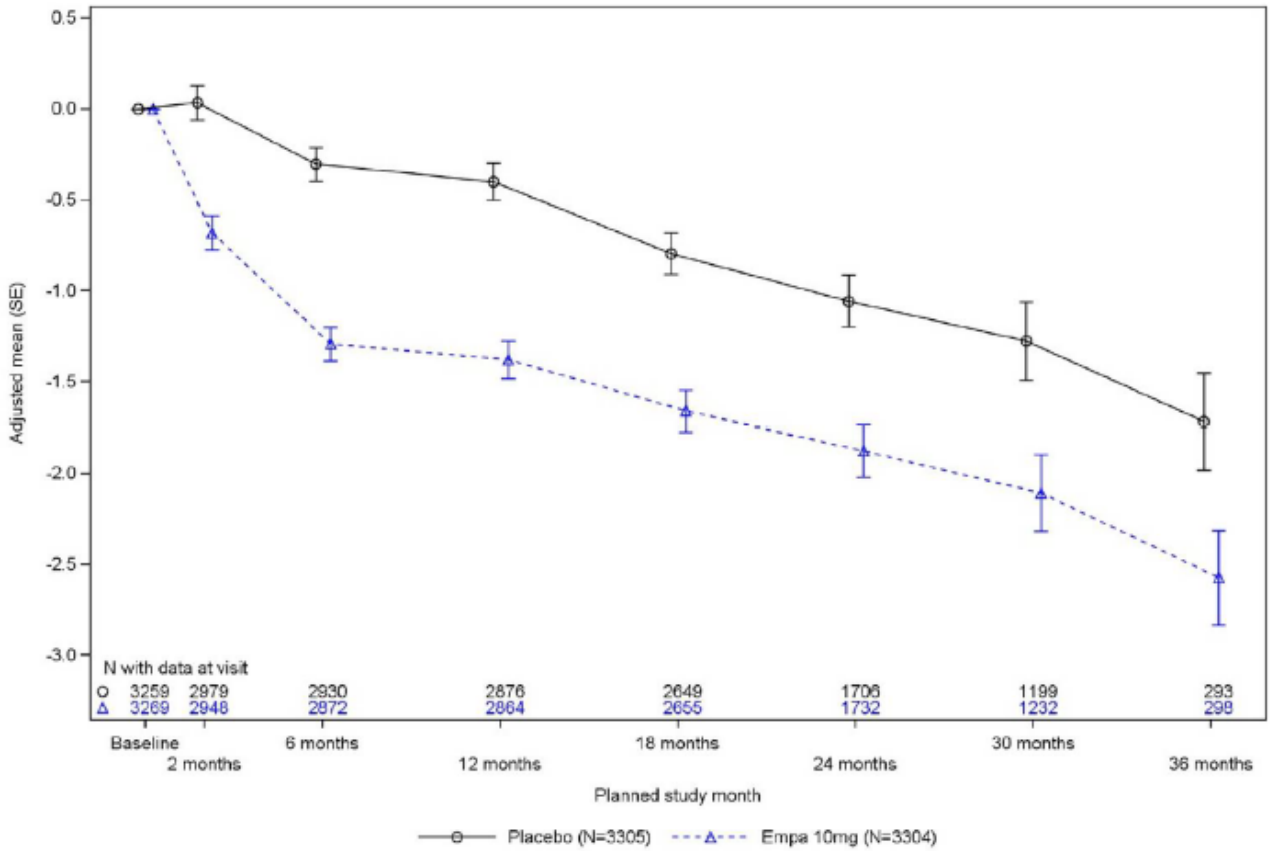
[1] Model included treatment as fixed effect.

Vital signs

- **Weight**

Participants in both treatment groups had decreases in weight over time. Average change from baseline over time in the empagliflozin group was -1.55 kg and was -0.68 kg in the placebo group (MMRM analysis; RS, OC-AD)

Figure 12. Weight (kg) change from baseline, MMRM results – RS (OC-AD)



- **Blood pressure**

Participants in both treatment groups had decreases in SBP and DBP over time. Average change from baseline over time in SBP was −3.9 mm Hg in the empagliflozin group and −1.3 mm Hg in the placebo group (MMRM analysis; RS, OC-AD). Average change from baseline over time in DBP was −1.6 mm Hg in the empagliflozin group and −1.2 mm Hg in the placebo group (MMRM analysis; RS, OC-AD).

Safety in special populations

Age

Subgroup analyses of adverse events by demographic and baseline characteristics were consistent with the overall AE profile. Further information is provided below for the analyses by age, baseline eGFR, and baseline UACR.

Table 54. AEs by age – TS

Category of AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Age <50 years	580 (100.0)		561 (100.0)	
Any AE	194 (33.4)	23.09	147 (26.2)	17.57
Leading to discont. of study medication	20 (3.4)	1.94	17 (3.0)	1.72
SAEs	128 (22.1)	13.72	104 (18.5)	11.69
Age 50 to <65 years	921 (100.0)		940 (100.0)	
Any AE	380 (41.3)	30.00	407 (43.3)	31.39
Leading to discont. of study medication	40 (4.3)	2.34	53 (5.6)	3.03
SAEs	274 (29.8)	19.06	293 (31.2)	19.88
Age 65 to <75 years	1044 (100.0)		1045 (100.0)	
Any AE	525 (50.3)	37.60	499 (47.8)	35.61
Leading to discont. of study medication	92 (8.8)	4.77	76 (7.3)	3.94
SAEs	414 (39.7)	26.76	384 (36.7)	24.34
Age >75	760 (100.0)		758 (100.0)	
Any AE	421 (55.4)	46.20	394 (52.0)	41.58
Leading to discont. of study medication	89 (11.7)	6.55	86 (11.3)	6.24
SAEs	351 (46.2)	33.51	307 (40.5)	28.48

eGFR status

Table 55. AEs by baseline eGFR – TS

Category of AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
eGFR <20 mL/min/1.73 m^2	131 (100.0)		123 (100.0)	
Any AE	75 (57.3)	50.41	63 (51.2)	45.47
Leading to discont. of study medication	30 (22.9)	14.10	8 (6.5)	3.99
SAEs	67 (51.1)	40.37	55 (44.7)	34.94
eGFR 20 to <30 mL/min/1.73 m^2	1020 (100.0)		1008 (100.0)	
Any AE	524 (51.4)	40.32	513 (50.9)	39.24
Leading to discont. of study medication	90 (8.8)	4.86	102 (10.1)	5.50
SAEs	408 (40.0)	27.25	396 (39.3)	26.64
eGFR 30 to <45 mL/min/1.73 m^2	1461 (100.0)		1467 (100.0)	
Any AE	678 (46.4)	34.30	623 (42.5)	30.83
Leading to discont. of study medication	98 (6.7)	3.61	99 (6.7)	3.69
SAEs	514 (35.2)	23.18	457 (31.2)	20.17
eGFR ≥45 mL/min/1.73 m^2	693 (100.0)		706 (100.0)	
Any AE	243 (35.1)	24.57	248 (35.1)	24.43
Leading to discont. of study medication	23 (3.3)	1.84	23 (3.3)	1.77
SAEs	178 (25.7)	16.41	180 (25.5)	16.23

Table 56. AEs by baseline UACR – TS

Category of AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Normal (UACR <30 mg/g)	663 (100.0)		665 (100.0)	
Any AE	337 (50.8)	38.91	315 (47.4)	35.94
Leading to discont. of study medication	51 (7.7)	4.05	55 (8.3)	4.52
SAEs	257 (38.8)	25.59	230 (34.6)	23.02
Microalbuminuria (UACR 30 to ≤300 mg/g)	937 (100.0)		927 (100.0)	
Any AE	445 (47.5)	35.43	403 (43.5)	32.31
Leading to discont. of study medication	64 (6.8)	3.74	75 (8.1)	4.43
SAEs	340 (36.3)	24.26	303 (32.7)	21.77
Macroalbuminuria (UACR >300 mg/g)	1705 (100.0)		1712 (100.0)	
Any AE	738 (43.3)	32.20	729 (42.6)	30.91
Leading to discont. of study medication	126 (7.4)	4.12	102 (6.0)	3.26
SAEs	570 (33.4)	22.28	555 (32.4)	21.12

Diabetes status

AEs according to diabetes status have been described for the AEs of special interest (AESI).

Discontinuation due to adverse events

The overall frequency of participants reported with AEs leading to discontinuation of study medication between treatment groups is provided in the table below. On the PT level, the most frequently reported AEs leading to discontinuation were coronavirus infection and sudden cardiac death. The most commonly reported AEs leading to discontinuation of study medication (>0.2%) in either treatment group at the PT level) are summarised in Table 57.

Table 57. Participants with AEs leading to discontinuation of study medication (frequency >0.2% in either treatment group at the PT level) – TS

MedDRA SOC	Placebo		Empa 10 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of participants	3305 (100.0)		3304 (100.0)	
Total with AEs leading to discontinuation	241 (7.3)	4.00	232 (7.0)	3.84
Infections and infestations	53 (1.6)	0.88	61 (1.8)	1.01
Coronavirus infection	21 (0.6)	0.35	18 (0.5)	0.30
Cardiac disorders	32 (1.0)	0.53	23 (0.7)	0.38
Ischaemic cardiomyopathy	7 (0.2)	0.12	11 (0.3)	0.18
Cardiac failure	10 (0.3)	0.17	7 (0.2)	0.12
General disorders and administration site conditions	29 (0.9)	0.48	26 (0.8)	0.43
Sudden cardiac death	17 (0.5)	0.28	12 (0.4)	0.20
Death	9 (0.3)	0.15	10 (0.3)	0.16
Renal and urinary disorders	22 (0.7)	0.36	19 (0.6)	0.31
End stage renal disease	11 (0.3)	0.18	9 (0.3)	0.15
Investigations	15 (0.5)	0.25	15 (0.5)	0.25
Blood creatinine increased	11 (0.3)	0.18	11 (0.3)	0.18

All serious and non-serious AEs leading to discontinuation of study medication were collected (Section 9.7.1.3.4).
If adjudicated, the resulting preferred terms are presented.

2.5.1. Discussion on clinical safety

An extensive number of patients have been included in this trial; 3304 patients treated with empagliflozin and 3305 with placebo, respectively, with a median exposure of 22 months and 91% treated for at least 1 year and 44% at least 2 years.

The overall safety profile appears reassuring and showed a slightly lower number of AEs for empagliflozin vs placebo (44% vs 46%), SAEs (33% vs 35%) and AEs leading to death (2.7% vs 2.8%) and appears to be well-tolerated with a lower rate of discontinuations due to AEs (7.0% vs 7.3%, mostly attributed to cardiac disorders (0.7% vs 1.0%) and coronavirus infection (0.5% vs 0.6%)). Moreover, no SAE according to SOC or single type of event was reported to be increased for empagliflozin vs placebo. Similarly, no specific AE category could be identified with increased AEs leading to death for empagliflozin. Further, the most frequently reported AEs were gout (7.0% vs 8.0%), acute kidney injury (2.8% vs 3.5%) and coronavirus infection (3.0% vs 3.2%) and did not reveal any new pattern in comparison to previous findings (in different populations). An overall presentation of the safety profile according to diabetes status did not reveal on any difference between both groups.

For several AEs of special interest due to the known safety profile of empagliflozin or (potential) safety issues as included in the RMP, including gout (8.2% vs 9.2%, 4.75 vs 5.35/100pt-yrs), serious hyperkalemia (2.6% vs 2.9%, 1.42 vs 1.62/100 pt-yrs), adjudicated liver injury (0.4% each, 0.22 vs 0.20/100pt-yrs), and serious urinary tract infections (1.3% vs 1.4%, 0.70 vs 0.78/100 pt-yrs) the event rates were comparable or lower for empagliflozin vs placebo, and do not raise for any safety concern.

Adjudicated cases of lower limb amputations (LLA) were slightly higher for empagliflozin (0.8% (n=26) vs 0.4% (n=14), 0.43 vs 0.23/100 pt-yrs), mainly occurred in patients with diabetes (1.5% (n=23) vs 1.1% (n=17; data of up-to-final follow-up) vs non-diabetes (0.15% (n=5) vs 0.06% (n=2; data of up-to-final

follow-up) and was mainly seen for toe amputation (0.5% vs 0.4%, 0.30 vs 0.22/100 pt-yrs). Based on Cox-regression analyses, only a numerical increase could be observed of HR 1.43 (0.80, 2.57). When 4 major trials were combined, the HR was also numerically increased with an HR 1.16 (0.86, 1.57), and a HR of 1.14 (0.84, 1.56) for the diabetic population. Any AEs potentially related to LLA were not consistent across the studies, which complicates the interpretation of these findings. A warning statement currently included in the SmPC shows that this has been observed with another SGLT-2 inhibitor but that it is not known whether it is a class effect. Based on the current data, no stronger conclusions can be drawn, and this is thus acceptable.

Volume depletion (3.0% vs 2.7%, 1.64 vs 1.51/100 pt-yrs) and symptomatic dehydration (2.4% vs 2.1%, 1.34 vs 1.17 100/pt-yrs) was slightly increased, although hypotension was seen at similar frequency (0.7% each).

Severe hypoglycemic events were comparable between treatment groups (2.2% each, 1.24 vs 1.21/100 pt-yrs), although 4 cases were observed in non-diabetic patients treated with empagliflozin (vs 0 in placebo). The relationship to empagliflozin remains unclear, as for these cases alternative confounders/explanations appear available.

Adjudicated cases of ketoacidosis occurred at a low frequency but increased for empagliflozin (6 (0.2%) vs 1 (<0.1%). Of these, one case of non-diabetic ketoacidosis occurred, which has not previously been described and associated to the use of empagliflozin (or any other SGLT-2 inhibitor). This concerned a 73 year-old woman with comorbidities of HF, CAD and CKD stage IV, who needed hospitalisation for AKI and ketoacidosis, and recovered after treatment discontinuation. Sections 4.4 and 4.8 of the SmPC are amended to include appropriate warnings accordingly.

In the current trial, these were slightly increased using different definitions of using user-defined (3.7% vs 3.2%, 2.04 vs 1.78/100 pt-yrs) and narrow BIcMQ definition up to trial completion (4.1% vs 3.7%, 2.06 vs 1.86/100 pt/yrs). The Cox-regression analysis did not reveal a higher incidence for empagliflozin (HR 1.08 (95% CI 0.84, 1.38)). The MAH did not present the data according to diabetes status.

Urinary tract malignancies up to trial completion were low and comparable for empagliflozin vs placebo (0.6% vs 0.5%, 0.28 vs 0.22/100pt-yrs), and do not reveal any signal.

Adjudicated cases of serious genital infection occurred in only 1 case in the empagliflozin group. This does not allow for any clear conclusions, but it has already been included as ADR in the labelling.

As showed in a trial subset of UK participants (437 vs 374), haemoglobin and haematocrit were increased for empagliflozin vs placebo (clinically significant abnormalities 1.8% vs 0.5% and 1.3% vs 0.5%, respectively). Haematocrit increase is already a known reversible effect of empagliflozin as already described in the product information. No differences of sodium-corrected calcium or phosphate were observed between treatment groups in this study subset.

No clear pattern for a different safety profile of empagliflozin vs placebo was observed according to age category (< 50, 50-65, 65-75, >75), except that the frequency of AEs was increased with increasing age. No clear pattern for a different safety profile of empagliflozin vs placebo was observed according to GFR category (< 20, 20-30, 30-45, >45), except that the frequency of AEs was increased with lower GFR category. No pattern of a different safety profile according to UACR category could be observed.

2.5.2. Conclusions on clinical safety

The pivotal trial provided as part of this application showed a safety profile that appears reassuring and showed that empagliflozin appears to be well tolerated also in a population at reduced renal function. In

general, the safety profile was as expected, except that one case of ketoacidosis was observed in a non-diabetic patient, which had not previously been observed for empagliflozin.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 20.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 20.1 with the following content:

Safety concerns

SVIII.Table 1 Summary of safety concerns

Important identified risks	None
Important potential risks	Urinary tract carcinogenicity ~~Amputation risk~~ Pancreatitis
Missing information	None

Pharmacovigilance plan

The MAH has removed the study PASS 1245.137 addressed to the important potential risk "Amputation risk" from the list of additional pharmacovigilance activities included in the pharmacovigilance plan.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires (T2DM indication) for:

- ~~Amputation risk (including events preceding amputation)~~
- Pancreatitis

Other forms of routine pharmacovigilance activities for:
None.

PART III.1 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Part III.1.1 PASS 1245-0097 summary

Study short name and title
1245-0097 - Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with T2DM: a multi-database European study

Rationale and study objectives
To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment

Study design
Observational, comparative, cohort safety study

Study population
Adult patients with T2DM

Milestones
Final report, 30 Sep 2023

~~**Part III.1.2 PASS 1245-0137 summary**~~

~~**Study short name and title**~~
~~1245-0137 - A multicentre international randomised parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease~~

~~**Rationale and study objectives**~~
~~To assess the effect of empagliflozin on time to kidney disease progression or cardiovascular death~~

~~**Study design**~~
~~Randomised, parallel group, double-blind, placebo-controlled trial~~

~~**Study population**~~
~~Adult patients with chronic kidney disease~~

~~**Milestones**~~
~~Final report, 31 Mar 2023~~

PART III.2 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

PIII.Table 1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS 1245-0097 Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with T2DM: a multi-database European study Ongoing	To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract carcinogenicity	Final report	30 Sep 2023
~~**PASS 1245-00137**~~ ~~A multicentre international randomised parallel group double blind placebo controlled clinical trial of EMPAgliflozin once daily to assess cardio renal outcomes in patients with chronic KIDNEY disease~~ ~~Ongoing~~	~~To assess the effect of empagliflozin on time to kidney disease progression or cardiovascular death~~	~~Amputation risk~~	~~Final report~~	~~31 Mar 2023~~

Risk minimisation measures

This part has been updated to remove data regarding the safety concern "Amputation risk".

RISK MINIMISATION PLAN

PART III.3 ROUTINE RISK MINIMISATION MEASURES

PIII.Table 2 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	
Important potential risks	

Urinary tract carcinogenicity	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Empagliflozin is available as prescription only medicine.
~~Amputation risk~~	~~*Routine risk communication*~~ ~~SmPC section 4.4, PL section 2~~ ~~*Routine risk minimisation activities recommending specific clinical measures to address the risk*~~ ~~None~~ ~~*Other routine risk minimisation measures beyond the Product Information*~~ ~~Empagliflozin is available as prescription only medicine.~~
Pancreatitis	*Routine risk communication* None *Routine risk minimisation activities recommending specific clinical measures to address the risk* None *Other routine risk minimisation measures beyond the Product Information* Empagliflozin is available as prescription only medicine.
Missing information	
None	

PART III.4 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part III.3 are sufficient to manage the safety concerns of the medicinal product.

PART III.5 SUMMARY OF RISK MINIMISATION MEASURES

PIII.Table 3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Urinary tract carcinogenicity	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* None *Additional pharmacovigilance activities* PASS 1245-0097 (final report 30 Sep 2023)
~~Amputation risk~~	~~*Routine risk minimisation measures*~~ ~~SmPC section 4.4~~ ~~PL section 2~~ ~~Prescription only medicine~~ ~~*Additional risk minimisation measures*~~ ~~None~~	~~*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection*~~ ~~AE follow-up form to capture data on patients with amputation risk~~ ~~*Additional pharmacovigilance activities*~~ ~~PASS 1245-0137 (final report, 31 Mar 2023)~~
Pancreatitis	*Routine risk minimisation measures* Prescription only medicine *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form to capture data on patients with pancreatitis. *Additional pharmacovigilance activities* None
Missing information		
None		

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The package leaflet for Jardiance was subject to a readability user testing with the initial marketing authorization application. Further, with the indication extension for heart failure with reduced ejection fraction (EMEA/H/C/002677/II/0055) a readablity user test was conducted. In the final report of February 2021, the package leaflet was rated readable and comprehensive. No further improvement was deemed necessary per this recent report. During procedure EMEA/H/C/002677/II/0055, the package leaflet was updated based on CHMP's request to ensure patient's understanding in the contexts of the side effect 'diabetic ketoacidosis'. With this proposed indication extension, the update of the package leaflet will only concern sections 1. 'What Jardiance is used for' and 'What is chronic kidney disease?' as well '4. Possible side effects'. The design and layout of the printed package leaflet will not change. Given that a readability user test was only conducted recently and that changes to be introduced with the new indication chronic kidney disease are only very limited in extent, it is considered justified to not consult with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem affecting 10-15% of the population worldwide. Chronic kidney disease results from a variety of causes, such as diabetes, hypertension, vascular disease, or glomerulonephritis. CKD is associated with excess risk for cardiovascular disease (CVD), and cardiovascular events are the most frequent cause of death in patients with CKD. In addition, high levels of albuminuria are associated with an increased risk of all-cause and cardiovascular mortality.

CKD is associated with impaired quality of life and substantially reduced life expectancy at all ages. End-stage renal disease (ESRD) is the most severe form of CKD and is fatal if not treated by renal replacement therapy. Although patients with early CKD are more likely to die before they reach ESRD, the avoidance of ESRD is still highly desirable due to its negative impact on quality of life and the substantial costs of dialysis and transplantation to healthcare providers.

3.1.2. Available therapies and unmet medical need

The standard of care for CKD in patients with and without diabetes is represented by blood pressure control and reduction of proteinuria through RAAS blockade (ACE-I or ARB) combined with CV risk management and/or and glycaemic control as necessary.

Although RAAS blockade has been shown to reduce albuminuria and slow the rate of progression in proteinuric nephropathies, particularly in diabetic kidney disease, a substantial residual risk of ESRD remains. Therefore, there is an unmet medical need for new treatment options that can be added safely to current standard treatments in CKD, with a primary aim of slowing the progression of CKD and reducing risk of CV death. Although, currently another SGLT2i, dapagliflozin, has already been indicated to be used in diabetic and non-diabetic patients with CKD based on the results of the DAPA-CKD study

(and additional evidence from other dapagliflozin studies) including a slightly more restricted population of patients with eGFR 25 to 90 ml/min/1.73m2 and albuminuria > 200 mg/g compared to current EMPA-KIDNEY inclusion.

3.1.3. Main clinical studies

The EMPA-KIDNEY (trial 1245.137) was a randomised, placebo-controlled, double-blind, parallel-group event-driven study to demonstrate superiority in slowing renal disease progression of empagliflozin 10 mg vs. placebo on top of guideline-directed medical therapy (including appropriate RASi background therapy) in a (broad) population generally at risk of kidney disease progression both with and without diabetes.

The study population was included based on either eGFR ≥20 <45 mL/min/1.73m2, or an eGFR ≥45 mL/min/1.73m2 with urinary albumin/creatinine ratio ≥200 mg/g (or protein/creatinine ratio≥300 mg/g). This does not include the entire CKD population as patients with eGFR 45 to 60 (and 60 to 90) ml/min/1.73m2 without albuminuria has not been included, likely due to a lower risk for renal disease progression and possibly relatively increased risk for CV events (depending on CV disease history).

The study was designed to test whether empagliflozin was superior to placebo for the primary endpoint of a composite of time to the first occurrence of kidney disease progression (defined as end-stage kidney disease [ESKD], a sustained decline in eGFR to <10 mL/min/1.73 m2, 'as adjudicated' renal death, or a sustained decline of ≥40% in eGFR from randomisation); or CV death ('as adjudicated'). Secondary endpoints that were tested using the Hochberg procedure were all-cause mortality, time to the first occurrence of HHF ('as adjudicated') or CV death ('as adjudicated'), and all-cause hospitalisations (first and recurrent combined).

This event-driven study was designed to have a power of 90% for the primary endpoint at a 2-sided α of 0.05 to detect an 18% relative reduction in the primary outcome, which required approximately 1070 primary outcome events.

The EMPA-KIDNEY trial was carried out at 241 clinical sites in 8 countries in North America, Europe, and Asia (United States, Canada, Germany, United Kingdom, Italy, China, Malaysia, and Japan). The trial included 6609 patients (3304 empagliflozin vs 3305 placebo). Baseline data were well balanced between the treatment groups. The majority of subjects were elderly (55% > 65 years) white male subjects (67%) with a mean eGFR of 37 mL/min/1.73 m2, and 52% having macro-albuminuria (>300 mg/g), and 54% being non-diabetic, representing a patient population at high risk of disease progression.

3.2. Favourable effects

Empagliflozin showed a significant superior effect for the primary endpoint of time to the first event of kidney disease progression or adjudicated CV death (432 (13.1%) vs 448 (16.9%); HR 0.72 (0.64, 0.82), p<0.001, which became evident after approximately 1 year of treatment. The primary endpoint was mainly driven by the eGFR reduction ≥40% surrogate (293 (8.9%) vs 373 (11.3%)), although every component demonstrated a lower number of events for empagliflozin during the study period. Consistency in all sensitivity analyses showed the robustness of the primary finding. Also, secondary and exploratory renal (composite) endpoints supported the major finding, including endpoints of time to first occurrence of kidney disease progression, time to different renal outcome definitions, a slower rate in eGFR change (slope), and slower annual rate for total slope and chronic slope. Further, the positive renal findings occurred before any CV effects emerged, with non-significant findings in overall mortality, CV mortality, CV endpoints (major CV events, time to HHF), and renal components driving the significance of any other combined renal/CV endpoints (time to CV death or ESKD). From a mechanistic point of view

and as previously observed, the initial drop in eGFR and greater reduction in UACR with empagliflozin are of further support.

The primary result was consistent across the key subgroup of baseline eGFR. In non-diabetic patients, the primary effect was slightly less apparent (HR 0.82 (0.68, 0.99) vs diabetic (HR 0.64 (0.54, 0.77), although the p-value for interaction did not reach significance (0.0598) and it should be noted that in both subpopulations a significant effect was observed. For albuminuria, a trend toward lower efficacy with lower albuminuria could be observed (p=0.0174), while no significant p-value for interaction was observed for UACR < vs ≥200 mg/g (HR 0.87 (0.66, 1.15) and 0.71 (0.62, 0.82), respectively (interaction p-value = 0.2090)).

A significant finding of a lower proportion of patients with the occurrence of all-cause hospitalisations (key secondary endpoint) was found, which may reflect the risk of disease burden and mortality. Further, a separation between renal and cardiovascular causes has been provided and show consistent beneficial effects.

A minor difference in reduction in HbA1c (-0.4 %) was observed. This may be expected, as the glucose-lowering effect of empagliflozin is eGFR dependent, thereby low in this population with reduced kidney function.

3.3. Uncertainties and limitations about favourable effects

For albuminuria, a trend toward lower efficacy with lower albuminuria could be observed (p=0.0174), while no significant p-value for interaction was observed for UACR < vs ≥200 mg/g (HR 0.87 (0.66, 1.15) and 0.71 (0.62, 0.82), respectively (interaction p-value = 0.2090)). In particular, in the normal to micro-albuminuria groups, absence or very limited efficacy appears to be present. A statement reflecting these findings is included in the SmPC.

A CKD population of patients with eGFR <20 ml/min/1.73m2 has been scarcely evaluated in the current study, while such patients were initially covered by the proposed extension of indication and dose recommendation. Therefore, initiating treatment in these patients would not be recommended. A statement reflecting treatment in this population is included in the SmPC.

A similar reduction of the primary composite endpoint in the empagliflozin group was seen independent of the aetiology of kidney disease, although patients with polycystic nephropathy and those receiving immunosuppressive medication were excluded (except prednisolone ≤10 mg or equivalent) .

Although the renal findings appear convincing (see favourable effects), a slightly larger decrease in body-weight (-1.6 kg vs -0.7 kg already at month 6 and approximately -2.7 kg vs -1.7 kg at 36 months) was observed compared to placebo. However, this was not caused by a decrease in muscle mass.

In general, demographics were well-balanced between the treatment groups in the trial. The majority of subjects was elderly (55% > 65 years) white male subjects (67%), with a sufficient proportion of patients have been included in Europe (40.1%). However, Black or African American patients may be considered underrepresented (4.0%).

Inclusion of patients without standard of therapy of RASi are limited in line with the inclusion criteria, but show comparable results on the primary endpoint.

3.4. Unfavourable effects

An extensive number of patients have been included in this trial; 3304 treated with empagliflozin and 3305 with placebo, respectively, with a median exposure of 22 months and 91% treated for at least 1

year and 44% at least 2 years. Importantly, additional exposure to patients with lower eGFR has now emerged, who were previously generally excluded based on the current SmPC recommendation (lower glucose-lowering efficacy), except for heart failure patients (≥ 20 ml/min/1.73 m2).

The overall safety profile appears reassuring and showed a slightly lower number of AEs for empagliflozin vs placebo (44% vs 46%), SAEs (33% vs 35%) and AEs leading to death (2.7% vs 2.8%) and appears to be well tolerated with a lower rate of discontinuations due to AEs (7.0% vs 7.3%, mostly attributed to cardiac disorders (0.7% vs 1.0%) and coronavirus infection (0.5% vs 0.6%)). Moreover, no SAE according to SOC or single type of event was reported to be increased for empagliflozin vs placebo. Similarly, no specific AE category could be identified with increased AEs leading to death for empagliflozin.

Most frequently reported AEs were gout (7.0% vs 8.0%), acute kidney injury (2.8% vs 3.5%) and coronavirus infection (3.0% vs 3.2%) and did not reveal any new pattern in comparison to previous trial findings.

No clear pattern for a different safety profile of empagliflozin vs placebo was observed according to GFR category (< 20, 20-30, 30-45, >45), except that the frequency of AEs was increased with lower GFR category as expected. No pattern of a different safety profile according to UACR category could be observed.

For several AEs of special interest due to the known safety profile of empagliflozin or potential safety issues as included in the RMP, including gout (8.2% vs 9.2%, 4.75 vs 5.35/100pt-yrs), serious hyperkalemia (2.6% vs 2.9%, 1.42 vs 1.62/100 pt-yrs), adjudicated liver injury (0.4% each, 0.22 vs 0.20/100pt-yrs), and serious urinary tract infections (1.3% vs 1.4%, 0.70 vs 0.78/100 pt-yrs) the event rates were comparable or lower for empagliflozin vs placebo, and do not raise for any safety concern. Further, urinary tract malignancies up to trial completion were low and comparable for empagliflozin vs placebo (0.6% vs 0.5%, 0.28 vs 0.22/100pt-yrs), and do not reveal any signal.

Adjudicated cases of ketoacidosis occurred at a low frequency but were increased for empagliflozin (6 (0.2%) vs 1 (<0.1%)). Of these, one case of non-diabetic ketoacidosis occurred, which has not previously been described and associated to the use of empagliflozin (or any other SGLT-2 inhibitor). This concerned a 73 year-old women with comorbidities of HF, CAD and CKD stage IV, who needed hospitalisation for AKI and ketoacidosis, and recovered after treatment discontinuation. Appropriate warnings have been added accordingly in sections 4.4 and 4.8 of the SmPC.

As based on a trial subset of UK participants (437 vs 374), haemoglobin and haematocrit were increased for empagliflozin vs placebo (clinical significant abnormalities 1.8% vs 0.5% and 1.3% vs 0.5%, respectively). Haematocrit increase is already a known reversible effect of empagliflozin as already described in the labelling. No differences of sodium, corrected calcium or phosphate was observed between treatment groups in this study subset.

3.5. Uncertainties and limitations about unfavourable effects

Adjudicated cases of lower limb amputations (LLA) were slightly higher for empagliflozin (0.8% (n=26) vs 0.4% (n=14), 0.43 vs 0.23/100 pt-yrs), mainly occurred in patients with diabetes (1.5% (n=23) vs 1.1% (n=17; data of up-to-final follow-up) vs non-diabetes (0.15% (n=5) vs 0.06% (n=2; data of up-to-final follow-up) and was mainly seen for toe amputation (0.5% vs 0.4%, 0.30 vs 0.22/100 pt-yrs). Based on Cox-regression analyses, only a numerical increase could be observed of HR 1.43 (0.80, 2.57). When 4 major trials were combined, the HR was also numerically increased with HR 1.16 (0.86, 1.57), and a HR of 1.14 (0.84, 1.56) for the diabetic population. Any AEs potentially related to LLA were not consistent across the studies, which complicates the interpretation of these findings. A warning statement in this

regard is already included in the SmPC to highlight that this has been observed with another SGLT-2 inhibitor, although it is not known whether it can be considered a class effect. Based on the current data, no stronger conclusions can be drawn, and this is thus acceptable.

Volume depletion (3.0% vs 2.7%, 1.64 vs 1.51/100 pt-yrs) and symptomatic dehydration (2.4% vs 2.1%, 1.34 vs 1.17 100/pt-yrs) were slightly increased, although hypotension was seen at similar frequency (0.7% each).

Severe hypoglycemic events were comparable between treatment groups (2.2% each, 1.24 vs 1.21/100 pt-yrs), although 4 cases were observed in non-diabetic patients treated with empagliflozin (vs 0 in placebo). The relationship to empagliflozin remains unclear, as for these cases alternative confounders/explanations appear available.

In the current trial, these were slightly increased using different definitions of using user-defined (3.7% vs 3.2%, 2.04 vs 1.78/100 pt-yrs) and narrow BIcMQ definition up to trial completion (4.1% vs 3.7%, 2.06 vs 1.86/100 pt/yrs). The Cox-regression analysis did not reveal a higher incidence of empagliflozin (HR 1.08 (95% CI 0.84, 1.38)).

Adjudicated cases of serious genital infection occurred in only 1 case in the empagliflozin group. This does not allow for any clear conclusions, but it has already been included as an ADR in the product information.

No clear pattern for a different safety profile of empagliflozin vs placebo was observed according to age category (< 50, 50-65, 65-75, >75, >85), except that the frequency of AEs was increased with increasing age.

3.6. Effects Table

Table 58. Effects Table for Jardiance

Effect	Short description	Unit	Empagliflozin (10 mg)	Control (Placebo)	Uncertainties / Strength of evidence	Ref
Favourable Effects						
Renal disease progression or CV death	Composite of ESKD, eGFR<10, renal death, eGFR≥40%, or CV death	N(%)	432 (13.1)	558 (16.9)	**SoE**: HR 0.72 (0.64, 0.82). Supported by secondary and exploratory renal (composite) endpoints (e.g. slower rate in eGFR change (slope) with 'crossing of lines'). Mechanistic support from initial drop in eGFR and greater reduction in UACR. **Unc**: Driven by the eGFR reduction ≥40% surrogate (293 (8.9%) vs 373 (11.3%))	EMPA-KIDNEY
HHF or CV death		N(%)	152 (4.6)	131 (4.0)	**Unc**: HR 0.84 (0.67, 1.07)	
All-cause hopitalisations	all-cause hospitalisations (first and recurrent combined)	N(%)	840 (25.4)	899 (27.2)	**SoE**: HR 0.86 (0.78, 0.95)	
Mortality	All-cause death	N(%)	148 (4.5)	167 (5.1)	**Unc**: HR 0.87 (0.70, 1.08)	
Unfavourable Effects						
SAEs	General serious adverse events	N (%)	1088 (32.9)	1167 (35.3)	**SoE**: No SAE according to SOC or single type of event increased for empa. Serious events of AESI of liver injury, AKI, gout, hyperkalemia, hypoglycemia, urinary tract infections, genital infection, urinary tract malignancy were lower or comparable.	

Effect	Short description	Unit	Empagliflozin (10 mg)	Control (Placebo)	Uncertainties / Strength of evidence	Ref
Ketoacidosis			6 (0.2%)	1 (<0.1)	**SoE**: one case observed in non-diabetic patient	
LLA	Lower limb amputation	N(%)	26 (0.8)	14 (0.4)	**SoE:** Most cases of toe amputation (0.5% vs 0.4%) **Unc**: OT HR 1.16 (0.86, 1.57), last-follow-up HR 1.05 (0.81, 1.36). Meta-analysis (4 studies) HR 1.16 (0.86, 1.57); Any AEs potentially related to LLA were not consistent across the studies	
Volume depletion			98 (3.0)	90 (2.7)	**SoE**: Symptomatic dehydration (2.4% vs 2.1%) **Unc**: HR 1.25 (0.73, 2.14), Hypotension (0.7% each)	
Bone fracture		N (%)	136 (4.1)	123 (3.7)	**Unc**: HR 1.08 (0.84, 1.38)	

Abbreviations: ESKD: End Stage Kidney Disease; HHF: Heart Failure Hospitalisation; CV: Cardiovascular

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CKD is a serious and progressive condition that is associated with CV disease and an increased risk of adverse outcomes. The most common cause of CKD is diabetes. Despite cornerstone therapy of RAAS inhibition with either ARBs or ACEi, patients with CKD, including those with diabetes, remain at high risk of developing ESRD and/or experiencing CV events.

Although some trends toward renal benefit have previously been observed in other studies with empagliflozin, the current dedicated renal study has demonstrated a renal benefit both in diabetes (T2DM) patients and non-diabetes patients. The latter observation is important as this provides a reason to make this explicit in the indication, as the currently authorised indication is focused on the beneficial effects in the diabetes population (except for HF). This would follow a similar approach as for the HF population (a specific indication granted), also including non-diabetics in the HF trials performed and be aligned with another SGLT-2 inhibitor (dapagliflozin), where a specific renal indication has been adopted based on results in a dedicated renal study in a population including DM and non-DM CKD patients. However, there was a CHMP discussion during the procedure about whether extrapolation to the entire CKD population was indeed justified (see further below).

The primary effect in the EMPA-KIDNEY study was observed even at the lower range of the GFR spectrum and without any signal for increased risk of acute kidney injury despite an initial drop in eGFR at start of treatment, thus supporting treatment even in patients with very low renal reserve (GFR >20 ml/min/1.73m2), which is even slightly lower than evaluated with dapagliflozin (> 25 ml/min/1.73m2). Although, it could be questioned whether the current data generated by the EMPA-KIDNEY study would sufficiently justify treatment across the full range of the CKD population as proposed in the current application, additional justification has been provided by the Applicant during the procedure. Based on studies previously submitted showing benefits in less advanced CKD patients, a meta-analyses of SGLT2i and extrapolation of data from a mechanistic point of view, such broad range seems reasonable and can be accepted. However, initiation of empagliflozin in the very low eGFR range of <20 ml/min/1.73m2, is not supported due to absence of data and possible safety issues., and thus the product information has been updated accordingly. The approach to accept the broad indication of ”treatment of CKD patients”

and to reflect any limitations of the available evidence in the SmPC, is in line with the product information of dapagliflozin.

Generally, the safety profile can be considered reassuring, and empagliflozin appears to be well tolerated with no evidence of increased discontinuation due to AEs. As mentioned, even in the lower eGFR range, the safety profile is reassuring, although obviously more adverse events occur in general in patients with lower GFR, without any clear signal for safety concerns.

Specific attention has been given to potential adverse effects associated with empagliflozin or based on previous safety findings in other populations with empagliflozin. Most remarkable is the finding of one case of ketoacidosis in a non-diabetic patient, which has not been observed previously and appropriate warnings have been included in the product information as this may typically not be anticipated in clinical practice. Further, the risk of lower limb amputation remains inconclusive based on current and previous studies' combined risk estimation. Overall, the proposal to remove this potential safety risk from the RMP can be endorsed since the two studies required to address this important potential risk have been completed and there is no reasonable expectation that any further pharmacovigilance activity can further characterise this risk to draw firm conclusions.

3.7.2. Balance of benefits and risks

Current positive findings on the primary renal effects in a general CKD population (including non-diabetic patients) at risk of disease progression are clinically relevant, although the effect was mainly driven by the eGFR reduction ≥40% surrogate. No unexpected safety concern arises from the current trial, except the fact that ketoacidosis could also occur in non-diabetic patients and the risk of LLA remains somewhat undetermined. However, the initiation of empaglifozin treatment in patients with CKD including those with eGFR < 20 ml/min/1.73m2 is not recommended, which is appropriately reflected in the SmPC.

3.8. Conclusions

The overall B/R of Jardiance in the treatment of Chronic Kidney Disease in adults is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, 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

Extension of indication to include treatment of chronic kidney disease (CKD) in adults, based on final results from study EMPA-KIDNEY (1245-0137) listed as a category 3 study in the RMP; this is a Phase III, multicentre international randomised parallel group double-blind placebo controlled clinical trial of empagliflozin once daily to assess cardio-renal outcomes in patients with chronic kidney disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is

updated in accordance. Version 20.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.