27 January 2022
EMA/102340/2022
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/0060

Note

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

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List of abbreviations

6MWT	6-minute walk test
ACEi	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
AELD	Adverse event leading to treatment discontinuation
AESI	Adverse event of special interest
AF	Atrial fibrillation or atrial flutter
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query (used where SMQ is not available)
BMI	Body mass index
CEC	Clinical event committee
CHQ-SAS	Chronic heart failure questionnaire self-administered standardised format
CI	Confidence interval
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CMH	Cochran-Mantel-Haenszel
CMR	Cardiac magnetic resonance
CO	Clinical overview
CPET	Cardiopulmonary exercise test
CRF	Case report form
CRT (-D/P)	Cardiac resynchronisation therapy (-defibrillator/pacemaker)
CTD	Common Technical Document
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Cardiovascular
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DMC	Data monitoring committee

ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
eGFR $(CKD\text{-}EPI)_{cr}$	Glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement
eGFR (MDRD)	Glomerular filtration rate estimated by the modification of diet in renal disease formula
EMPA-VISION	A mechanistic trial of empagliflozin on cardiac physiology and metabolism in patients with chronic heart failure; trial 1245.148
EMPERIAL	Trials of empagliflozin on exercise ability and heart failure symptoms in patients with chronic heart failure; EMPERIAL-preserved: trial 1245.167; EMPERIAL-reduced: trial 1245.168
EMPEROR	Outcome trials of empagliflozin in patients with chronic heart failure; EMPEROR-reduced: trial 1245.121; EMPEROR-preserved: trial 1245.110
ERA	Environmental risk assessment
FU	Follow up
GCP	Good clinical practice
gMean	Geometric mean
HF	Heart failure
HFD	High fat diet
HFmEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalisation for heart failure
HL	Hodges-Lehmann
ICD	Implantable cardioverter defibrillator
ICH	International conference on harmonisation
IQR	Interquartile range
ISS	Integrated summary of safety
ITT	Intent to treat
KCCQ	Kansas City cardiomyopathy questionnaire
LLA	Lower limb amputation
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MDA	Malondialdehyde

MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MMRM	Mixed model repeated measure
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York heart association
OC-AD	Observed case including data after treatment discontinuation
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic(s)
PEC	Predicted environmental concentration
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PT	Preferred term
pt-yrs	Patient-years
qd	Once daily
RS	Randomised set
SAE	Serious adverse event
SAF-HF1	Safety analysis grouping for trials in patients with heart failure (1245.110, 1245.121, 1245.148, 1245.167, 1245.168)
SBP	Systolic blood pressure
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SCR	Screened set
SD	Standard deviation
SEM	Standard error of measurement
SGLT	Sodium-dependent glucose co-transporter
SMQ	Standardised MedDRA query
SOC	System organ class
SOP	Standard operating procedures
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

TIA	Transient ischaemic attack
TS	Treated set
TSAP	Trial statistical analysis plans
TSS	Total symptom score
ULN	Upper limit of normal
UTI	Urinary tract infection
WCI	Worst-case imputation

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 26 August 2021 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 add the treatment of patients with Heart Failure with preserved ejection fraction based on the results from the clinical study 1245.110 EMPEROR-preserved.
As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and sections 1 and 4 of the PIL are updated accordingly.
Further, the MAH applied for an additional year of market protection. The updated RMP v 16.0 has also been submitted.
In addition, the statement 'sodium free' was re-located from section 2 of the SmPC to section 4.4. to comply with EMA'S QRD guidance and minor linguistic changes to the national translations are included in this submission

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

Information on paediatric requirements

Not applicable

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 August 2021
Start of procedure:	18 September 2021
CHMP Rapporteur Assessment Report	15 November 2021
PRAC Rapporteur Assessment Report	19 November 2021
PRAC Outcome	2 December 2021
CHMP members comments	6 December 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 December 2021
Request for supplementary information (RSI)	16 December 2021
PRAC Rapporteur Assessment Report	12 January 2022
CHMP Rapporteur Assessment Report	12 January 2022
Updated CHMP Rapporteur Assessment Report	20 January 2022
Opinion	27 January 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues, or the heart can only provide adequate blood supply at the expense of elevated left ventricular filling pressure. HF occurs due to failure of the heart to pump adequately (systolic dysfunction) and/or impaired relaxation (diastolic dysfunction).

State the claimed the therapeutic indication

The claimed indication that is under assessment reads as follows (in bold the proposed extension of the indication):

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure **independent of left ventricular** ~~with reduced~~ ejection fraction.

In the first assessment round, the CHMP concluded that the wording of the indication should be adjusted.

As the indication for the treatment of heart failure is for all types of heart failure, the wording *"for the treatment of symptomatic chronic heart failure"* was considered more appropriate. In the response, the Applicant has adjusted the wording of the indication in accordance with the comments.

The approved indication reads as follows (in strikethrough the proposed extension of the indication):

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure ~~with reduced ejection fraction~~.

Epidemiology and risk factors

Worldwide, heart failure has a prevalence of 1% to 2% and affects over 64 million people as of 2017. In the US alone the prevalence is 6.2 million, and this number has been projected to grow to over 8 million by 2030. HF is associated with premature mortality and frequent hospitalisations. HF contributes to 1 in 9 deaths, and the estimated 5-year survival is about 50% at the time of diagnosis. In addition, HF is the leading cause of hospitalisation in patients above 65 years of age. In the US, more than 1 million patients annually are hospitalised with a primary diagnosis of HF.

Clinical presentation, diagnosis

Symptoms of HF include dyspnoea (shortness of breath), oedema (build-up of fluid in the body tissues), persistent coughing and wheezing (due to build-up of fluid in the lungs), tiredness or fatigue, reduced appetite or nausea, confusion, disorientation, and increased heart rate. The most commonly used classification system, the New York Heart Association (NYHA) Functional Classification, places patients in one of four categories based on how much they are limited during physical activity. The classes range from I, i.e. no limitation of physical activity, to IV, i.e. unable to carry on any physical activity without discomfort.

Patients with HF are categorised according to left ventricular ejection fraction (LVEF); patients with LVEF ≤40% are considered to have HFrEF, and those with LVEF >50% are considered to have HFpEF. LVEF of >40% to <50% is considered as HFpEF in many clinical trials and registries, although more recently, the term HF with "mid-range" EF (HFmEF) was introduced to categorise this group separately. The relative prevalence of HFpEF among HF patients is approximately 50% and appears to be increasing.
HFrEF and HFpEF differ in several aspects, including underlying aetiologies, demographics, co-morbidities, and responses to treatment. For example, patients with HFpEF tend to be older, more often women, and more likely to have a history of hypertension and atrial fibrillation than patients with HFrEF. In addition, although HFpEF and HFrEF have similarly profound impacts on patient quality of life and prognosis, historically, therapies shown to improve prognosis in patients with HFrEF do not seem to be effective in patients with HFpEF.

In addition to a substantial risk of mortality and hospitalisation, HF is shown to have a major impact on all aspects of quality of life, and particularly on patients' mobility and usual activities. Poor quality of life scores independently predicts higher mortality and hospitalisation. Despite guideline-directed medical therapy, the quality of life in patients with HF remains greatly impaired.

Management

Heart failure with a reduced ejection fraction can be treated with drugs that attenuate the overactivation of endogenous neurohormonal systems. However, the therapeutic options for patients with heart failure and a preserved ejection fraction are limited.

Recommendations for the treatment of HFrEF include the use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA), and the use of implantable devices like ICD and CRT, all of which have been shown to reduce mortality in patients with HFrEF.

For patients with HFpEF, no therapy has been proven to be superior to control based on the pre-specified primary endpoint in any prior pivotal clinical outcome study in patients with HFpEF. According to the current guidelines, the management of HFpEF involves controlling congestive symptoms, usually with diuretics, and treating co-morbidities. A lack of therapeutic options that can reduce the risk of mortality and hospitalisation in these patients represents an unmet medical need.

2.1.2. About the product

Empagliflozin (Jardiance) is an orally administered, potent and selective inhibitor of the human sodium-glucose cotransporter-2 (SGLT 2) developed by Boehringer Ingelheim (BI). By inhibition of SGLT 2 in the kidneys, empagliflozin reduces the reabsorption of glucose by the kidneys leading to increased urinary glucose excretion and, consequently, to a lowering of blood glucose. Empagliflozin is approved for the treatment of type 2 diabetes mellitus (T2DM) worldwide as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes. In the United States and several other countries, it is also approved to reduce the risk of cardiovascular (CV) death in patients with T2DM and established CV disease. The results of the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) showed significant improvement in the primary composite cardiovascular outcome (MACE-3) and significant reductions in cardiovascular death, hospitalization for heart failure (HHF) as well as death from any cause as compared to standard of care. These beneficial cardiovascular effects were found to be largely independent of the glucose-lowering effect of empagliflozin. On 17 Jun 2021, empagliflozin was approved in the EU for the treatment of heart failure with reduced ejection fraction based on the EMPEROR-Reduced study (1245.121) results.

Empagliflozin exerts its effect by preventing sodium and glucose reabsorption. While natriuresis will be compensated within days of drug administration through changes in tubulo-glomerular feedback, glucosuria will last for as long as the medication is used. This leads to long-lasting hemodynamic changes associated with modest osmotic diuresis, blood pressure-lowering effect, improvement in arterial stiffness, reduction in oxidative stress, and decrease in rate pressure product, an indirect measure of myocardial oxygen demands, with no increase in HR and no effect on sympathetic nerve activity. Therefore, the non-glycosuric physiological and hemodynamic adaptations under empagliflozin may benefit patients with HF with or without diabetes.

Based on the results of trial 1245.25 (EMPA-REG OUTCOME) in patients with T2DM and established CV disease, BI initiated a phase III program for empagliflozin 10 mg once daily in chronic heart failure regardless of diabetes status.

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

The development programme

BI initiated a Phase III program for empagliflozin 10 mg once daily in chronic heart failure regardless of diabetes status. There are two CV outcome trials ("EMPEROR"), two functional capacity trials ("EMPERIAL"), and a mechanistic Phase III trial ("EMPA-VISION") in patients with HFrEF (reduced ejection fraction) and HFpEF (preserved ejection fraction). All 5 trials are placebo-controlled, randomised (empagliflozin 10 mg

to placebo 1:1), double-blind, and parallel-group by design.

The EMPEROR trials are pivotal outcome trials that investigate the long-term effect of empagliflozin in reducing the risk of hospitalisation for HF and of cardiovascular death in patients with heart failure. The EMPERIAL trials are additional trials that investigated the short-term (12 weeks) effect of empagliflozin on functional capacity, signs and symptoms of heart failure, and quality of life. The EMPA-VISION trial is a supporting trial investigating the short-term (12 weeks) effect of empagliflozin on mechanistic cardiac physiology and metabolism. All 5 trials have been completed and the clinical trial reports are available.

The EMPEROR-Reduced and the EMPERIAL trials have been previously submitted. The EMPEROR-Preserved trial results are described in this document. In addition, a meta-analysis of both EMPEROR trials for efficacy endpoints was prespecified.

Compliance with CHMP guidance

The most relevant CHMP guideline is "Clinical investigation of medicinal products in the treatment of chronic heart failure" (CPMP/EWP/235/95, Rev.2). The compliance with this guideline is addressed in the discussion of the design of the trial.

Scientific advice

The Applicant requested scientific advice for both the EMPEROR-preserved and EMPEROR-reduced trial in procedure in 2016, Procedure No.: EMEA/H/SA/2969/2/2016/II.

2.1.4. General comments on compliance with GLP, GCP

GLP

Not applicable

GCP

According to the Applicant, the trials are carried out in compliance with the CTP, in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH GCP, and in accordance with applicable regulatory requirements and BI's standard operating procedures.

2.2. Non-clinical aspects

2.2.1. Introduction

Empagliflozin is approved in many countries globally as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes, and to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin significantly improved the primary composite cardiovascular outcome (MACE-3: composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke) and significantly reduced cardiovascular death, hospitalization for heart failure (HHF) as well as death from any cause as compared to standard of care. In the EMPEROR-Reduced trial, empagliflozin significantly improved cardiovascular and renal outcomes in patients with heart

failure with reduced ejection fraction, independent of baseline diabetes status. Interestingly, these beneficial cardiovascular effects were found to be largely independent of the glucose-lowering effect of empagliflozin.

The beneficial cardiovascular effects of empagliflozin in clinical studies may result – at least in part - from an influence on neurohumoral pathways, such as RAAS inhibition via tubulo-glomerular feedback mechanisms and from a reduction of cardiac pre- and afterload by natriuretic and osmotic effects. Further, an increased haematocrit, decrease in blood pressure and cardiac sympathetic nerve activity have been observed with empagliflozin and may contribute to the effects on the cardiovascular system.

Effects of empagliflozin on pathophysiological processes in the cardiovascular system were studied in various pharmacological experimental settings, in particular in models of heart failure induced by different stimuli. Furthermore, effects of empagliflozin were studied *in vitro* in cardiac tissue of patients with HFpEF, respectively, as well as in tissues taken from mice.

In vivo studies were performed in different species like mice, rats and pigs 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 cardiovascular system. Importantly, studies were done in normoglycemic animals and in animals with pre-existing diabetes.

This document is an Addendum to the Nonclinical Overview [U12-3933-01] submitted with the initial Marketing Authorization Application (MAA). Since the initial MAA, three nonclinical study reports with the corresponding Addendum to Nonclinical Overview were submitted to provide:

- results of a nonclinical study looking at the effect of empagliflozin on blood ketone level at refeeding after a fasting period and comparison between refeeding with glucose or fat [n00253114-01]

- results of an *in vitro* study investigating the inhibition of UGT2B7, UGT1A3, UGT1A8, and UGT1A9 by empagliflozin [n00234868-01]

- results from a nonclinical juvenile toxicity study in the rat [n00231757-01].

Empagliflozin is a SGLT2 inhibitor that reduces the reabsorption of glucose by the kidney resulting in the increased urinary glucose excretion and subsequent lowering of the blood glucose. Empagliflozin also showed beneficial cardiovascular effects in the clinical trials with patients with heart failure, which appear to be independent of its glycaemic control action. Empagliflozin is currently approved for the treatment of patients with heart failure with reduced ejection fraction (HFrEF). The current application concerns the extension of the indication to the patients with heart failure with preserved ejection fraction (HFpEF). The applicant has submitted an addendum (dated 29 July 2021) to the previously provided non-clinical overview, including the pre-clinical studies conducted to investigate the cardiovascular effects of empagliflozin in vitro *in vivo*, to provide the rationale for the envisaged extension. As the clinical effects were shown to be independent of the well-documented glucose-lowering effects of empagliflozin, the pre-clinical studies were performed in normoglycaemic animals as well as in animals with pre-existing diabetes mellitus. The addendum was prepared by Dr. Michael Paul Pieper and consists of 17 pages with 23 references. The CV of Dr. Pieper has been provided.

2.2.2. Pharmacology

Primary pharmacodynamic studies

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 empagliflozin reduces the reabsorption of glucose by the kidneys

leading to increased urinary glucose excretion and, in consequence, to a lowering of blood glucose under hyperglycaemic as well as normoglycemic conditions.

The results of the EMPA-REG OUTCOME trial as well as the EMPEROR-Reduced trial clearly demonstrated the beneficial effects of empagliflozin on the cardiovascular system.

In this section, pre-clinical studies are compiled that investigated the cardiovascular effects of empagliflozin *in vitro* and *in vivo* in various species and different experimental settings. As the clinical effects were shown to be independent of the well-documented glucose-lowering effects of empagliflozin, the pre-clinical studies were performed in normoglycemic animals as well as in animals with pre-existing diabetes mellitus.

Effects of empagliflozin *in vitro/ex vivo*

Potential direct effects of 500 nmol/L empagliflozin on myocardial tissue were investigated in LV myocardial biopsies obtained from patients with HFpEF and compared to samples from non-failing hearts [P20-04305]. Inflammation markers including ICAM-1, VCAM-1, TNF-a, and IL-6 were higher in human HFpEF myocardium than controls. Empagliflozin significantly reduced the inflammatory markers assessed both by ELISA and immunoblots. Empagliflozin lowered the pathophysiologically increased cardiomyocyte Ca^{2+}-independent passive force ($F_{passive}$), a measure for cardiomyocyte stiffness, in cardiomyocytes from patients with HFpEF *in vitro*. GSH administration resulted in a further additional effect on $F_{passive}$. In contrast, empagliflozin did not induce additional effects on $F_{passive}$ on top of GSH indicating an antioxidative effect of empagliflozin in cardiomyocytes.

Experiments were performed in murine papillary muscles from diabetic BKS.Cg-Dock7m +/+ Leprdb/J mice showing a typical diabetic cardiomyopathy phenotype [P18-09844]. Empagliflozin significantly reduced the excessive diastolic tension by ~19.1 % in these isolated organs *in vitro*. This effect was reversible upon wash-out.

Thus, empagliflozin caused direct effects on the myocardium of patients with HFpEF and similar effects in mice with diabetic cardiomyopathy by improving diastolic stiffness that may translate in an improved diastolic function. Furthermore, empagliflozin reduced myocardial inflammation and oxidative stress in cardiomyocytes from patients with HFpEF compared to tissue from non-failing hearts.

Effects of empagliflozin on endothelial dysfunction and cardiac remodelling were tested in obese Zucker diabetic fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1)-HFpEF rats, experimentally used as a model of metabolic syndrome. Rats develop a dysfunction in endothelium-dependent relaxations and cardiac remodelling. Lean rats were used as controls [P20-01824]. Rats were treated with empagliflozin via a diet admixture at a daily dose of 30 mg/kg for 6 weeks. *Ex vivo*, empagliflozin restored the normal endothelium-dependent relaxations and blunted endothelium-dependent contractile responses to acetylcholine. Further, empagliflozin reduced the increased heart weight as well as the increased left ventricle volume in ZSF1 rats. Interestingly, SGLT2 protein expression was detected in vascular endothelial cells under stress conditions in this model.

Effects of empagliflozin in animals with diabetes:

Effects of empagliflozin on diabetic cardiovascular injury was tested in male db/db mice and male nondiabetic and lean db/m mice as control [P14-15469]. Mice were fed a standard diet containing 0.03% empagliflozin for 10 weeks. Empagliflozin significantly ameliorated cardiac interstitial fibrosis, peri-coronary arterial fibrosis, coronary arterial thickening, cardiac interstitial macrophage infiltration, and cardiac superoxide levels in db/db mice. Further, empagliflozin significantly ameliorated the impairment of vascular endothelial function compared with control db/db mice.

In summary, empagliflozin ameliorated cardiac fibrosis, inflammation, coronary arterial remodelling, and vascular dysfunction in db/db diabetic mice.

Effects of empagliflozin on cardiovascular function was tested in db/db mice on a high fat diet as a model of severe type 2 diabetes [P20-03987]. Mice were fed a high fat western-type diet (high fat diet (HFD), 39 kJ% fat, 41 kJ% carbohydrates and 20 kJ% protein) with or without 150 mg/kg empagliflozin. Empagliflozin induced glycosuria and reduced blood glucose levels. The increased expression of hepatic inflammatory cytokines in db/db mice was significantly reduced by empagliflozin treatment. Empagliflozin reduced mortality in db/db mice: while 54 % of db/db mice on HFD died after 4.5 weeks, all heterogeneous wild type mice as well as all empagliflozin-treated db/db mice on HFD were alive. Hemodynamic investigations revealed that empagliflozin significantly improved cardiac relaxation as an indicator of diastolic function while numerically affecting systolic left ventricular function. Heart rate was unaffected by empagliflozin. No change in ketone bodies or branched-chain amino acids were observed in this study.

In summary, empagliflozin improved diastolic cardiac function and reduced mortality in db/db mice on a high fat diet.

Effects of empagliflozin on myocardial oxidative stress and fibrosis were tested in the genetic type 2 diabetic KK-Ay mouse model [P19-01258]. Levels of blood glucose levels as well as HbA1c levels in mice were significantly decreased by empagliflozin after 8 weeks of treatment. After 8 weeks of HFD, the LV mass/body weight ratio in mice with diabetes mellitus (DM) was significantly lower than that in control and diabetic mice treated with empagliflozin (DM+EM). Empagliflozin treatment largely restored the ejection fraction (EF), the fractional shortening (FS), the fractional area change (FAC), and the ratio between early (E)-to-late (A) diastolic mitral inflow (E/A ratio) in DM mice, which were similar to those in the control group. LV mass was decreased in all of the diabetic groups compared with the control group. However, the LV mass/body weight ratio in DM mice was significantly lower than that in control and DM + EM mice. Empagliflozin inhibited the reduction of left ventricular internal dimension in diastole (LVIDd) and decreased interventricular septum thickness in diastole (IVSd) as compared to the control group. There were, however, no significant differences in the values of left ventricular internal dimension in systole (LVIDs) and interventricular septum thickness in systole (IVSs) among the three groups. In the DM group, lipid hydroperoxide concentration and malondialdehyde (MDA) level were significantly higher than in control and DM + EM groups treated with empagliflozin. Furthermore, decreased levels of the antioxidant enzymes SOD and GSHPx were restored by empagliflozin. Thus, empagliflozin almost completely inhibited the increase in MDA that is considered a biomarker of oxidative stress.

DM mice showed a massive accumulation of extracellular matrix and myocardial fibrosis demonstrated by histology using Masson's trichrome staining as well as immunohistochemistry. Empagliflozin inhibited the increase in TGF-ß1-, collagen type I-, collagen type III- and connective tissue fraction- positive areas as compared to DM mice significantly.

Thus, empagliflozin inhibited LV dysfunction and remodelling and inhibited myocardial fibrosis and oxidative stress in the type 2 diabetic KK-Ay mice model.

Echocardiography in obese diabetic rats (ZDF) revealed a mild diastolic dysfunction (HFpEF) in comparison to their lean controls [P18-09844]. A prolonged isovolumetric relaxation time (IVRT), reduced E/A ratio and mild cardiac hypertrophy (increased wall thickness) was observed in the diseased rats. Empagliflozin after intravenous injection of 0,25 mg/kg significantly shortened IVRT (to 27.0±3.6 ms) and increased E/A ratio (to 1.6±0.4), indicating an improved diastolic function. The systolic contractile function as measured by ejection fraction was not altered. Further, the microvascular inflammation was reduced by empagliflozin in ZDF rats [P20-04305]. Empagliflozin reduced markers for oxidative stress, namely H2O2, 3-nitrotyrosine, and lipid peroxide and restored the antioxidant GSH to control levels. The NO–sGC–cGMP–PKG pathway was restored as well.

In summary, empagliflozin improved functional parameters of heart failure, induced anti-inflammatory as well as anti-oxidative effects and restored the NO bioavailability *in vivo*.

Cardiac energy deficiency is characterized by a decreased cardiac phosphocreatinine-to–ATP ratio (PCr/ATP) and has been proposed to play a major role in the development of heart failure. Male diabetic C57BL/Ks db/db mice received a single oral dose of empagliflozin (30 mg/kg) after 4 hours of fasting [P18-09761]. After further 2 hours of fasting plasma glucose and ketone levels (ß-hydroxybutyrate) were measured. Thereafter in vivo cardiac PCr/ATP and function were measured using 31P magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI), respectively. Empagliflozin lowered plasma glucose and increased plasma ketone levels compared to placebo-treated mice. Cardiac PCr/ATP ratio was 45% higher in empagliflozin-treated mice compared to placebo. Empagliflozin reduced this ratio to a value measured in nondiabetic db/+ mice in a separate study. The cardiac PCr/ATP ratio correlated with plasma ketone but not with plasma glucose levels. Empagliflozin-treated mice showed a lower end-diastolic and stroke volume compared with placebo, whereas ejection fraction and end-systolic volume were not significantly affected.

In summary, the increase in plasma ketone levels by a single oral dose of empagliflozin is associated with an improvement of cardiac energetics and cardiac function in fasting diabetic db/db mice, suggesting a role for ketones in the energy supply in cardiometabolic health.

Effects of empagliflozin in animals without diabetes:

As clinical studies indicate that empagliflozin exerts beneficial cardiovascular effects independently of the glucose-lowering effects, pre-clinical pharmacological studies in HF models were performed in animals without diabetes mellitus.

There are multiple ways to induce heart failure in pre-clinical experimental settings, e.g. HF secondary to myocardial infarction (MI) induced by ischemia-reperfusion or ligation/occlusion of coronary arteries, HF induced by transverse aortic constriction (TAC) and by injections of the anti-cancer compound doxorubicin all of them demonstrating aspects of the human heart failure pathophysiology.

Doxorubicin is a marketed drug for the treatment of different types of cancer. A serious, well-known side effect of doxorubicin is dilated cardiomyopathy, leading to congestive heart failure. Thus, Doxorubicin is experimentally used to induce cardiomyopathy in different animal models. Doxorubicin-induced cardiotoxicity is characterized by left ventricular dysfunction and cardiac hypertrophy, which lead to congestive HF. *In vivo* experiments were performed after a single administration of doxorubicin as well as after repeated administration for 12 days [P19-10933]. In both settings, mice were randomized into 4 groups, each: Control group, empagliflozin-treated group, control group + doxorubicin, empagliflozin-treated group + doxorubicin. For compound administration, mice were fed a normal chow diet containing 300 mg/kg empagliflozin. Empagliflozin reduced doxorubicin-induced myocardial fibrosis in mouse hearts as histologically demonstrated by Masson's trichrome staining in both acute and chronic settings. Mouse hearts showed hypertrophic changes after 12 days of doxorubicin treatment. Empagliflozin significantly improved ejection fraction, reduced fractional shortening, left ventricular diastolic and systolic dimension and significantly reduced LV mass compared with the sham-treated doxorubicin group. Serum levels of ketone bodies, namely ß-hydroxybutyrate (ßOHB), were significantly elevated in empagliflozin-treated mice with or without single doxorubicin injection.

In order to investigate the effects of ketones (ßOHB), H9C2 cardiac myocytes were treated with ßOHB at concentrations of 100 µM, 1 mM, 10 mM and 30 mM *in vitro* and exposed to 5 µM doxorubicin. The doxorubicin increased ROS production in H9C2 cells was significantly decreased by pretreatment with ßOHB for 2 hours. Further, ßOHB restored the doxorubicin-induced decrease of tetramethylrhodamine methyl ester (TMRM). This result suggests that ßOHB protects cardiomyocytes from doxorubicin-induced mitochondrial dysfunction. Finally, ßOHB significantly increased intracellular levels of ATP in H9C2 cardiac myocytes.

Effects of ßOHB were thereafter tested in vivo in single-dose doxorubicin-induced cardiomyopathy in mice. ßOHB preserved myofibril structure and reduced cardiac fibrosis in the left ventricles of mice exposed to doxorubicin.

In summary, empagliflozin attenuated doxorubicin-induced cardiomyopathy in mice. Doxorubicin-induced cardiac hypertrophy and myocardial fibrosis was reduced in empagliflozin diet-fed mice in the acute and chronic setting. Empagliflozin increased serum levels of ketone bodies. Ketone bodies were shown to induce cardioprotective effects. Thus, this study provides evidence that increased levels of ketone bodies may mediate these beneficial effects of empagliflozin.

Effects of empagliflozin on left ventricular dysfunction were tested in non-diabetic male Sprague–Dawley rats with myocardial infarction (MI) induced by permanent coronary artery ligation. Control rats underwent sham surgery [P19-03653]. Rats received a chow containing empagliflozin resulting in an average intake of 30 mg/kg/day or a control chow. Treatment started either 2 days before (early) or 2 weeks after surgery (late). Rats were stratified according to left ventricular ejection fraction (LVEF) 2 weeks post-surgery to ensure similar baseline cardiac function between the groups. The average infarct size in the left ventricle was 33 % and did not differ between the MI groups. MI induced a significant dilatation of the left ventricle and a reduction in LVEF. LVEF was significantly higher in both empagliflozin early and empagliflozin late group as compared to the respective sham-treated MI groups. Thus, empagliflozin prevented the progressive deterioration of cardiac function after MI. After MI, a marked cardiac hypertrophy was observed with a 10 % increase in ventricular mass and an 81 % increase in cardiomyocyte cross-sectional area. Empagliflozin attenuated the increase in LV mass both after early and late treatment and diminished the cardiomyocyte cross-sectional area compared to the sham-treated MI group.

The three-fold increase in myocardial fibrosis in the non-infarcted left ventricle was also markedly attenuated by empagliflozin treatment. Empagliflozin-induced reductions in fibrosis were paralleled by similar reductions in the expression of the fibrosis markers collagen 1 and pro-collagen.

Empagliflozin restored mitochondrial DNA (mtDNA) damage, increased mtDNA/nuclear DNA ratio and restored PGC1-αα expression, a critical mediator of mitochondrial biogenesis, indicating an attenuation of mitochondrial dysfunction. Cardiac ATP levels were significantly reduced in the MI-vehicle group and were significantly restored in the MI-EMPA-early group, and there was a trend towards increased ATP levels in the MI-EMPA-late group.

While the glucose and fatty acid oxidation is disrupted in the failing heart, ketone bodies are increasingly utilized as a fuel source. Empagliflozin increased circulating ketone levels and urinary ketone excretion in sham and MI groups. In parallel, ketone utilization was increased by empagliflozin as measured by expression of proteins involved in myocardial ketolysis: Ketone body transporter (MCT1), ketogenic enzyme ββ-hydroxy butyrate dehydrogenase (BDH1) and succinyl-CoA:3-ketoacid CoA transferase (SCOT).

In summary, empagliflozin improved cardiac function and remodelling in non-diabetic rats with LV dysfunction after MI. This effect was associated with substantial improvements in cardiac energy production measured as increased ATP levels.

Heart failure was induced in nondiabetic, female Yorkshire pigs by 2-h balloon occlusion of the proximal left anterior descending (LAD) artery followed by reperfusion [P19-03216]. Myocardial damage was confirmed by 3-dimensional (3D) echocardiography and cardiac magnetic resonance (CMR). Animals were then randomized to receive either 10 mg empagliflozin daily orally or placebo for 2 months. After this treatment period, 3D echo and CMR were repeated. Simultaneous blood samplings from coronary arteries and coronary sinus were performed to assess myocardial metabolite consumption and to calculate myocardial oxygen consumption and myocardial work efficiency. Tissue samples were collected for the assessment of myocardial energetics and molecular markers of cardiac metabolism.

Animals in the treatment group showed marked glycosuria demonstrating effective SGLT 2 inhibition in the kidneys of non-diabetic pigs. Empagliflozin ameliorated adverse cardiac remodelling and HF. In detail, empagliflozin reduced LV end-systolic and end-diastolic volumes detected with CMR and 3D echocardiography. Further, mean LV mass measured by both CMR and direct weight immediately after necropsy and the 3D-sphericity index were significantly lower in the empagliflozin-treated animals compared to the control group. Two months post-MI, control animals showed a myocardial metabolic switch characterized by marked reduction in FFA and enhanced glucose consumption compared to the non-MI group. Glucose was mainly metabolized through anaerobic metabolism, as confirmed by increased net myocardial lactate production. Empagliflozin modified the cardiac energy metabolism by switching away from glucose towards ketone bodies and free fatty acids as a source of energy. Empagliflozin-treated animals exhibited higher myocardial ATP (adenosine triphosphate) content. In summary, empagliflozin improved LV systolic and diastolic function and ameliorated adverse LV remodelling. This effect is likely to be - at least in part - mediated by switching the energy metabolism towards ketone bodies and free fatty acids, thus improving cardiac energy supply in pigs with heart failure secondary to myocardial infarction.

Empagliflozin is a SGLT2 (sodium-glucose transport protein 2) inhibitor that reduces the reabsorption of glucose by the kidney resulting in increased urinary glucose excretion and subsequent lowering of the blood glucose. Empagliflozin also showed beneficial cardiovascular effects in patients with heart failure, which appear to be independent of its glycaemic control action. The pharmacological mechanism of this effect is, however, not completely elucidated. In order to justify the proposed extension of the indication to the patients with heart failure with preserved ejection fraction (HFpEF) the applicant has provided an addendum to the previously provided nonclinical overview, consisting of public literature data that investigated the effects of empagliflozin on the cardiac function in myocardial samples of HFpEF patients, as well as in various pharmacological models of heart failure in different species (mice, rats and pigs). The investigations included both normoglycemic animals and animals with pre-existing diabetes.

SGLT2 inhibitors reduce blood glucose concentrations by inhibiting the main glucose transporter on the luminal surface of the proximal tubule in the kidneys, thus increasing urinary glucose excretion. The process works as a co-transport of glucose molecules and sodium ions (ratio 1:1), resulting in an increased concentration of sodium in the distal tubule and at the macula densa. Regulatory processes at the macula densa may influence neurohormonal pathways, such as RAAS inhibition, which together with a reduction of cardiac pre- and afterload by natriuretic and osmotic effects, may at least partially explain the beneficial cardiovascular effects of empagliflozin observed in clinical studies.

The provided literature overview demonstrated that in cardiomyocytes from the LV myocardial samples obtained from patients with HFpEF empagliflozin was shown to reduce the inflammation markers (ICAM-1, VCAM-1, TNF-α and IL-6) compared to the samples from non-failing hearts and attenuated pathological oxidative parameters (H_2O_2, 3-nitrotyrosine, GSH, lipid peroxide) in the cardiomyocytal cytosol and mitochondria's. The observed effects were explained as being possibly related to the reduced inflammation and oxidative stress due to the improved eNOS phosphorylation and NO bioavailability in the myocardium, as empagliflozin was demonstrated to increase the NO levels, sGC activity, sGMP concentration and PKGIα activity. Empagliflozin was also shown to reduce cardiomyocyte stiffness, measured as cardiomyocyte Ca^{2+}-independent passive force (Fpassive), in cardiomyocytes from patients with HFpEF and in the treated in vivo murine ZDF obese rats, used as a model of HFpEF. In db/db mice on a high fat diet used as a type 2 diabetes mellitus model, empagliflozin improved left ventricular function and reduced mortality. Empagliflozin also improved functional parameters like ejection fraction, fractional shortening and the ratio between early (E)-to-late (A) diastolic mitral inflow (E/A ratio) in the genetic T2DM KK-Ay mouse model. In non-diabetic animals empagliflozin improved cardiac function in models of heart failure in ischemia/reperfusion-induced myocardial infarction in pigs, in doxorubicin-induced heart failure in mice and in coronary artery ligation-induced heart failure in rats. Further, empagliflozin increased the plasma levels

of ketone bodies, namely ß-hydroxybutyrate, which have been suggested to play a role as an alternative fuel for failing hearts with less oxygen consumption compared to glucose oxidation.

In summary, beneficial cardiovascular effects of empagliflozin have been demonstrated *in vitro* in cardiac tissue of patients with HFpEF, as well as in a number of animal heart disease models, both in normoglycemic and in diabetic animals. However, the exact molecular mechanism of the beneficial effects of empagliflozin in these in vitro/ex vivo models remains unclear. It could be related to increasing tubuloglomerular feedback and reducing intraglomerular pressure lowering both pre- and postload of the heart, and downregulating of sympathetic activity. Other contributing mechanisms, such as reduced inflammation and oxidative stress and the increased plasma levels of ketone bodies, can also not be excluded.

2.2.3. Pharmacokinetics

No new information has been provided.

2.2.4. Toxicology

No new information has been provided.

2.2.5. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) for empagliflozin was submitted with the initial MAA and an updated ERA after the 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 (heart failure in patients with preserved ejection fraction, HFpEF) 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 heart failure indication (HFpEF) with a much smaller patient group are considered negligible and well covered by the used Fpen.

In previously submitted procedures, a full ERA of empagliflozin was submitted, including the determination of physical-chemical properties, Phase I and, due to the exceeded PECsw threshold limit (of 0.125), also the Phase II environmental fate studies. The conclusion of this ERA was that empagliflozin is neither PBT nor vPvB, and no unacceptable adverse effects for the surface water, groundwater, STP (sewage treatment plant) and sediment are expected from the prescribed use of empagliflozin. According to the MAH, the ERA submitted with the initial MAA remains valid for the current type II variation covering the additional proposed indication. It is agreed with the MAH that, considering the lower maximum recommended dose, the PEC/PNEC ratios for the surface water, groundwater and STP will not increase more than twice and will therefore still be below the threshold level for Tier B (ratios for the single indication were 0.00052, ≤0.0000125 and ≤0.000003125). Still, the MAH was requested to submit an updated ERA table with the new PECsurfacewater value. The summary ERA table submitted with the initial MAA was updated with the new PECsurfacewater values. The MAH was also requested to amend the ERA table by deleting the data on

readily biodegradability and adding information data on persistence derived in the water/sediment study. Additionally, the MAH was requested to include data on toxicity to sediment dwelling organisms.

The summary ERA table which was included in the original authorization of Jardiance was updated by the MAH as requested (see table below).

Summary of 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)	0.225	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

2.2.6. Discussion on non-clinical aspects

The current application concerns an extension of the indication of Jardiance to patients with heart failure with preserved ejection fraction (HFpEF). The active substance empagliflozin is a SGLT2 (sodium glucose transport protein 2) inhibitor that reduces the reabsorption of glucose by the kidney resulting in the

increased urinary glucose excretion and subsequent lowering of the blood glucose. Empagliflozin also showed beneficial cardiovascular effects in patients with heart failure, which appear to be independent of its glycaemic control action. The pharmacological mechanism of this effect is, however, not completely elucidated. The applicant has provided an addendum to the previously submitted non-clinical overview based on public literature data that demonstrated beneficial cardiovascular effects of empagliflozin in vitro in cardiac tissue of patients with HFpEF and in a number of animal heart disease models, both in normoglycemic and in diabetic animals. It has been concluded that these effects could be related to increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and postload of the heart, and downregulating of sympathetic activity. Other contributing mechanisms, such as reduced inflammation and oxidative stress and the increased plasma levels of ketone bodies, can also not be excluded.

It is agreed with the MAH that the ERA conclusions based on the previous ERA of empagliflozin remain unchanged. The DT50-values for the total system, sediment and water normalised to 12 °C for empagliflozin and the relevant transformation products M3, M1 and M12 are included in the updated ERA as well as the proposed molecular structures of M3 and M1. It is also mentioned in the ERA that M3 is proposed to be a stereoisomer of the active substance empagliflozin and thus might be pharmacologically active. The MAH was however asked to submit an updated ERA table with the new PECsurfacewater value, deletion of the data on readily biodegradability and addition of information data on persistence derived in the water/sediment study and data on toxicity to sediment dwelling organisms.

2.2.7. Conclusion on the non-clinical aspects

Although several factors have been mentioned that may contribute to the positive actions of empagliflozin on heart function, the precise molecular mechanisms of these effects are not clear. Several possible mechanisms may play a role, such as a reduced sodium reabsorption in the proximal tubules, resulting in reduced intraglomerular pressure and lowered cardiac pre- and afterload; increased level of ketone bodies, improving cardiac energy supply by increasing cardiac uptake and oxidization of β-hydroxybutyrate. 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 provided information is endorsed.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of empagliflozin.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH (Table 1).

Table 1. Tabular overview of clinical studies

Trial no.	Phase	No. randomised	Patient population	Treatment duration	First patient screened	Last patient completed	CTR
CV outcome trials ("EMPEROR-Preserved/Reduced")							
1245.121	III	3730	HFrEF (LVEF ≤40%)	Event-driven	Apr 2017	May 2020	[c28576542]
1245.110	III	5988	HFpEF (LVEF >40%)	Event-driven	Mar 2017	Apr 2021	[c31803238]
Functional capacity trials ("EMPERIAL-preserved/reduced")							
1245.168	III	312	HFrEF	12 weeks	Mar 2018	Oct 2019	[c26554767]
1245.167	III	315	HFpEF	12 weeks	Apr 2018	Oct 2019	[c26554599]
Mechanistic cardiac physiology and metabolism ("EMPA-VISION")							
1245.148	III	72	HFrEF/HFpEF separate cohorts	12 weeks	Mar 2018	May 2020	[c31537568]

2.3.2. Pharmacokinetics

No new information has been provided with regard to basal pharmacokinetics. This is all described in previous applications.

Additionally, pharmacokinetic data from trial 1245.110 was compared with the data from trial 1245.121. As a measure of systemic drug exposure to empagliflozin, steady-state trough PK samples were taken in the EMPEROR-preserved trial in a subset of patients (overall number of patients with valid PK samples: N=519). The PK of empagliflozin in patients with chronic heart failure with preserved ejection fraction in the EMPEROR-preserved trial was presented. Additionally, pharmacokinetic data from trial 1245.110 was compared with the data from trial 1245.121.

Comparison of PK trial 1245.110 and 1245.121

After demographic and baseline characteristic stratifications, similar results were observed in patients with HFpEF when compared to patients with HFrEF: Empagliflozin exposure in both trials increased with a decrease in renal function or an increase in age and decreased with an increase in body weight or BMI. There were only minor differences in empagliflozin exposures between trials regarding all further demographic or baseline characteristics.

For all subgroups, the gMean steady state trough concentrations of empagliflozin 10 mg in trial 1245.110 were similar (0.71 to 1.24-fold) to those of empagliflozin 10 mg in trial 1245.121.

Table PK01 *Fold differences in the gMean steady state trough concentrations of empagliflozin trial 1245.110 with respect to those in trial 1245.121 for different subgroups.*

stratification by	**subgroup**	**1245.110 gMean (gCV[%]), N**	**1245.121 gMean (gCV[%]), N**	**Ratio gMean 1245.110 vs. gMean 1245.121**
	All	63.4 (80.6), 519	67.3 (91.8), 308	0.94
Intrinsic factors				
eGFR	≥ 90 mL/min/1.73 m^2	38.5 (109), 30	42.1 (84.6), 40	0.91
	≥60 and <90 mL/min/1.73 m^2	54.0 (78.7), 222	51.9 (92.3), 119	1.04
	≥30 and <60 mL/min/1.73 m^2	73.3 (68.0), 242	92.5 (72.4), 125	0.79

	≥ 15 and <30 mL/min/1.73 m^2	116 (75.9), 25	103 (62.6), 24	1.13
Age	< 50 years	48.5 (101), 12	40.9 (95.0), 22	1.19
	≥ 50 and < 65 years	52.8 (94.1), 68	58.4 (98.5), 84	0.90
	≥ 65 and < 75 years	64.0 (83.3), 189	67.8 (82.0), 112	0.94
	≥ 75 years	66.9 (72.8), 250	86.1 (84.6), 90	0.78
Body Weight	≤50 kg	87.6 (69.4), 40	90.4 (84.6), 34	0.97
	>50 and ≤70 kg	69.1 (72.4), 191	73.6 (89.2), 126	0.94
	>70 and ≤90 kg	57.5 (86.8), 164	63.1 (80.3), 101	0.91
	>90 kg	56.7 (82.1), 124	49.3 (113), 47	1.15
BMI	< 25 kg/ m^2	70.3 (68.2), 201	74.7 (83.4), 160	0.94
	≥ 25 and < 30 kg/ m^2	62.9 (94.4), 158	62.9 (95.6), 88	1.00
	≥ 30 and < 35 kg/ m^2	56.3 (89.3), 83	61.0 (81.7), 43	0.92
	≥ 35 kg/ m^2	55.7 (69.5), 77	46.5 (164), 17	1.20
Sex	Male	62.7 (81.3), 322	67.2 (88.5), 243	0.93
	Female	64.4 (79.5), 197	67.9 (105), 65	0.95
stratification by	**subgroup**	**1245.110 gMean (gCV[%]), N**	**1245.121 gMean (gCV[%]), N**	**Ratio gMean 1245.110 vs. gMean 1245.121**
Race	All	63.4 (80.6), 519	67.3 (91.8), 308	0.94
	Asian	71.0 (66.5), 235	68.9 (82.2), 172	1.03
	Black	65.6 (59.9), 21	63.9 (76.2), 13	1.03
	White	58.4 (88.6), 246	65.8 (114), 110	0.89
	Other	44.8 (132), 16	63.4 (55.6), 13	0.71
Lifestyle				
Smoking Status	Current Smoker	77.5 (65.1), 37	62.4 (63.0), 39	1.24
	Ex-Smoker	59.7 (76.3), 273	68.4 (92.1), 150	0.87
	Never Smoked	66.1 (87.7), 209	66.7 (101), 113	0.99
Alcohol status	Drinks Alcohol	62.2 (76.1), 245	66.6 (89.7), 107	0.93
	Does not Drink Alcohol	64.4 (84.6), 274	68.6 (90.4), 192	0.94
Background disease and Co-medication				
T2DM status	Non−T2DM	60.5 (74.3), 281	63.5 (94.4), 145	0.95
	T2DM	66.9 (87.5), 238	71.0 (89.2), 163	0.94
NYHA classification	I	63.6 (53.6), 3	not reportable	---
	II	62.1 (79.9), 438	68.6 (91.4), 240	0.91
	III	70.9 (84.9), 78	63.0 (94.2), 67	1.13
ARNi use at baseline	With ARNi	71.9 (80.6), 18	63.3 (101), 52	1.14
	Without ARNi	63.1 (80.6), 501	68.2 (90.0), 256	0.93

--- not calculated
[Source data: c36415368, Tables Z.11.3: 2-6, Tables Z.11.3: 8-9, Tables Z.11.3: 11-12, Table Z.11.3: 14, and Tables Z.11.3: 16 to 17]

In general pharmacokinetic data generated for EMPEROR-Preserved/ study is comparable to previously collected pharmacokinetic data.

Empagliflozin exposure in trial 1245.110 increased with a decrease in renal function (up to a 3.01-fold difference in gMean) or an increase in age (up to a 1.38-fold difference in gMean); This increase in exposure is correlated as average renal function decreases with an increase in age. In addition, empagliflozin exposure decreased with an increase in body weight (up to a 1.54-fold difference in gMean) or BMI (up to a 1.26-fold difference in gMean).

After demographic and baseline characteristic stratifications, similar results were observed in patients with HFpEF compared to patients with HFrEF. In addition, there were no differences (<1.25-fold difference in gMean) in empagliflozin exposure by sex, race (comparison Asian versus White or Black versus White), NYHA classification, diabetes status or use of ARNi at baseline.

Differences in empagliflozin exposures were observed among different groups of geographic region (up to 1.38-fold difference in gMean) or investigator country (up to a 1.44-fold difference in gMean).

However, when all data from special groups were compared with results from trial 1245.121, the gMean steady-state trough concentration of empagliflozin 10 mg was not higher than that of empagliflozin 25 mg in any corresponding subgroup in 1245.25 [c32077394]. Since the gMean steady-state trough concentrations were similar between 1245.110 and 1245.121 in all subgroups, these data support that dose adjustment based on PK is not needed for renal function, age, body weight, BMI, sex, race, smoking status, or alcohol use.

2.3.3. Pharmacodynamics

Mechanism of action

There were no new dedicated clinical pharmacology studies.

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. As the predominant transporter, it is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia, a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuronic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium, resulting in osmotic diuresis and reduced intravascular volume.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta-cell function and insulin pathway, and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta-cell function, including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by diuresis, which may contribute to sustained and moderate reduction of blood pressure. Empagliflozin may impact on multiple pathophysiological pathways common for both HFrEF and HFpEF. Empagliflozin reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing tubuloglomerular feedback and reducing intra-glomerular pressure, lowering both pre- and afterload of the heart, downregulating

sympathetic activity, and reducing left ventricular wall stress as evidenced by lower NT-proBNP values with further beneficial effects on cardiac remodelling, filling pressures and diastolic function.

The exact molecular mechanisms of the beneficial cardiovascular effects of empagliflozin are, however, still under intense pharmacological investigation.

2.3.4. Discussion on clinical pharmacology

Pharmacodynamics

The mode of action and pharmacodynamics of SGLT2i for the treatment of T2DM, in general, are well known. For the treatment of HFrEF, modes of action have also been described and discussed in a previous application. For HFrEF, it is thought that SGLT2i reduce sodium reabsorption, increase tubuloglomerular feedback and consequently lower both pre- and afterload of the heart and downregulating sympathetic activity. The Applicant also described mechanisms of action relevant for both HFrEF and HFpEF, e.g. reduction in left ventricular wall stress with further beneficial effects on cardiac remodelling, filling pressures and diastolic function.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Not applicable.

Based on the data for the indication of T2DM and HFrEF it is acceptable that no dose-finding study has been performed, but it cannot be excluded that a lower dose than 10 mg is effective for the current indication.

2.4.2. Main study(ies)

BI initiated a Phase III program for empagliflozin 10 mg once daily in chronic heart failure regardless of diabetes status. There are two CV outcome trials ("EMPEROR"), two functional capacity trials ("EMPERIAL"), and a mechanistic Phase III trial ("EMPA-VISION") in patients with HFrEF (reduced ejection fraction) and HFpEF (preserved ejection fraction). All 5 trials are placebo-controlled, randomised (empagliflozin 10 mg to placebo 1:1), double-blind, and parallel-group by design (Table 2.).

The EMPEROR trials are pivotal outcome trials investigating the long-term effect of empagliflozin in reducing the risk of hospitalisation for HF and cardiovascular death in patients with heart failure. The EMPERIAL trials are additional trials that investigated the short-term (12 weeks) effect of empagliflozin on functional capacity, signs and symptoms of heart failure, and quality of life. The EMPA-VISION trial is a supporting trial investigating the short-term (12 weeks) effect of empagliflozin on mechanistic cardiac physiology and metabolism. All 5 trials have been completed and the clinical trial reports are available.

The EMPEROR-Reduced and the EMPERIAL trials have been previously submitted. The EMPEROR-Preserved trial results are described in this document, along with a brief summary of EMERIAL and EMPA-VISION and the pre-specified meta-analysis of efficacy endpoints based on both EMPEROR trials. Safety assessments in this document mainly focuses on pooled results from all 5 trials.

Based on the results of the pivotal trial 1245.110 (EMPEROR-Preserved), BI sought a new indication for empagliflozin in adult patients with heart failure (NYHA class II-IV) with preserved ejection fraction.

Where the indication for patients with heart failure with reduced ejection fraction has already been approved (which was based on the previously submitted pivotal trial 1245.121, EMPEROR-Reduced), BI aims to

combine both indications to an indication for adult patients with symptomatic chronic heart failure (NYHA class II-IV).

Table 2. Clinical trials in patients with chronic heart failure

Trial no.	Phase	No. randomised	Patient population	Treatment duration	First patient screened	Last patient completed	CTR
CV outcome trials ("EMPEROR-Preserved/Reduced")							
1245.121	III	3730	HFrEF (LVEF ≤40%)	Event-driven	Apr 2017	May 2020	[c28576542]
1245.110	III	5988	HFpEF (LVEF >40%)	Event-driven	Mar 2017	Apr 2021	[c31803238]
Functional capacity trials ("EMPERIAL-preserved/reduced")							
1245.168	III	312	HFrEF	12 weeks	Mar 2018	Oct 2019	[c26554767]
1245.167	III	315	HFpEF	12 weeks	Apr 2018	Oct 2019	[c26554599]
Mechanistic cardiac physiology and metabolism ("EMPA-VISION")							
1245.148	III	72	HFrEF/HFpEF separate cohorts	12 weeks	Mar 2018	May 2020	[c31537568]

Title of Study: EMPEROR-preserved (1245.110)

Methods

Study participants

Trial 1245.110 was carried out at 622 clinical sites in 23 countries in Europe, Latin America, North America, Asia, and other (South Africa, Australia, India). In total, 5988 patients were randomised to double-blind empagliflozin 10 mg (2997 patients) or placebo (2991 patients) once daily treatment. Randomisation was stratified by region, diabetes history, LVEF, and eGFR (CKD-EPI)cr at screening. All but 3 randomised patients (1 in the empagliflozin 10 mg group and 2 in the placebo group) were treated with at least 1 dose of study medication.

Inclusion criteria

The key eligibility criteria for the EMPEROR-Preserved (1245.110), in comparison with EMPEROR-Reduced (1245.121), are shown in Table 3.

Table 3. Key eligibility criteria for the EMPEROR trials

1245.121 (HFrEF)	1245.110 (HFpEF)
Age ≥18 years Chronic HF NYHA class II to IV eGFR $(CKD\text{-}EPI)_{cr}$ ≥20 mL/min/1.73 m^2	

Reduced EF (LVEF ≤40%) and elevated NT-proBNP for patients with/without atrial fibrillation or atrial flutter (AF): LVEF / NT-proBNP without AF / NT-proBNP with AF 36 to 40% / ≥2500 pg/mL / ≥5000 pg/mL 31 to 35% / ≥1000 pg/mL / ≥2000 pg/mL ≤30% / ≥600 pg/mL / ≥1200 pg/mL ≤40% and HHF ≤12 months* / ≥600 pg/mL / ≥1200 pg/mL * For patients not meeting the categories above	Preserved EF (LVEF >40%) and elevated NT-proBNP: >300 pg/mL for patients without AF; >900 pg/mL for patients with AF Structural heart disease or HHF ≤12 months
Stable therapy for HF consistent with local and international cardiology guidelines	Appropriate and stable dose of oral diuretics if prescribed

NYHA, New York heart association; LVEF, left ventricular ejection fraction; HHF, hospitalisation for heart failure; AF, atrial fibrillation or atrial flutter; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR $(CKD\text{-}EPI)_{cr}$, glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement

Exclusion criteria

Patients were excluded if they had a disorder that could change their clinical course, independent of heart failure, or if they had any condition that might jeopardize patient safety or limit their participation in the trial. The key exclusion criteria are listed below.

Cardiovascular diseases or treatments that increase the unpredictability of or change the patients' clinical course, independent of heart failure

- Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischemia or new ischemic ECG changes), coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or transient ischemic attack in the past 90 days
- Heart transplant recipient or listed for a heart transplant. Currently implanted left ventricular assist device.
- Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. hemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction.
- Any severe (obstructive or regurgitant) valvular heart disease, expected to lead to surgery during the trial period
- Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomization
- Implanted cardioverter defibrillator within 3 months prior to screening
- Cardiac resynchronization therapy

Untreated or undertreated cardiovascular conditions that might influence the course of heart failure or tolerability of the study medications

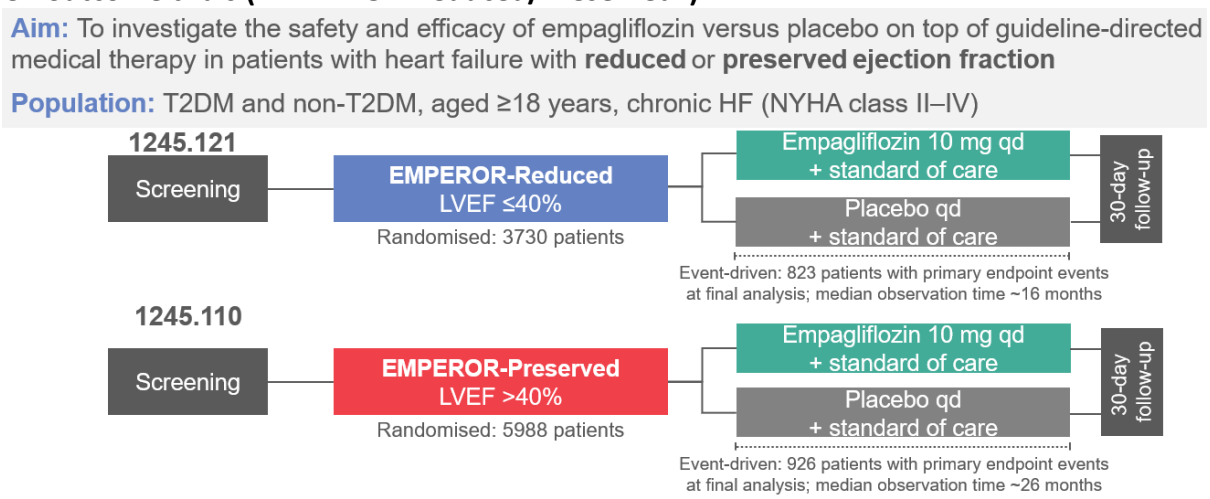
- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by ECG at screening
- Systolic blood pressure ≥180 mmHg at randomization. If the systolic blood pressure is 151-179 mmHg, the patient should be receiving ≥3 antihypertensive drugs
- Symptomatic hypotension and/or a systolic blood pressure <100 mmHg at screening or at randomization Significant comorbid conditions that might influence the clinical course, independent of heart failure
- Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalisation for exacerbation within 12 months; significant chronic pulmonary disease; or primary pulmonary arterial hypertension
- Acute or chronic liver disease, defined by serum levels of transaminases or alkaline phosphatase more than three times the upper limit of normal at screening
- Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 (CKD-EPI) or requiring dialysis at the time of screening
- Haemoglobin <9 g/dL at screening
- Major surgery (major according to the investigator's assessment) performed within 90 days prior to screening, or major scheduled elective surgery (e.g. hip replacement) within 90 days after screening.
- Gastrointestinal surgery or gastrointestinal disorder that could interfere with trial medication absorption.
- Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low risk prostate cancer (patients with pre-treatment PSA <10 ng/mL, and biopsy Gleason score of ≤6 and clinical stage T1c or T2a)
- Presence of any other disease than heart failure with a life expectancy of less than one year (in the opinion of the investigator) Any condition that might jeopardize patient safety, limit the patients' participation in the trial, or undermine the interpretation of trial data.

Treatments

Trial 1245.110 is a placebo-controlled, randomised (empagliflozin 10 mg to placebo 1:1), double-blind, and parallel-group by design. Patients were to be treated with randomised study medication in addition to standard of care (in accordance with local/international guidelines) until the required number of patients with adjudicated primary endpoint events was expected to be reached. The median observation time of the trial was about 26 months, with the median exposure to study medication about 23 months. After the last intake of study medication, patients were to be followed up for 30 days.

Design of EMPEROR trials in patients with chronic heart failure

CV outcome trials ("EMPEROR-Reduced/Preserved")



qd, once daily; LVEF, left ventricular ejection fraction; 6MWT, 6-minute walk test; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test

Objectives

The EMPEROR-Preserved trial is a pivotal CV outcome trial that investigates the long-term effect of empagliflozin in reducing the risk of hospitalisation for HF and of cardiovascular death in patients with HFpEF. The objective of this event-driven trial is to demonstrate the superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms.

Outcomes/endpoints

The following endpoints were pre-specified for 1245.110:

- Primary endpoint (confirmatory):
  - Time to first event of adjudicated CV death or adjudicated HHF
- Key secondary endpoints (confirmatory):
  - Occurrence of adjudicated HHF (first and recurrent)
  - eGFR (CKD-EPI)cr slope of change from baseline
- Other secondary endpoints (exploratory):
  - Time to the first event in the composite renal endpoint: chronic dialysis[1], renal transplant, or sustained[2] reduction in eGFR (CKD-EPI)cr[3]
  - Time to first adjudicated HHF
  - Time to adjudicated CV death
  - Time to all-cause mortality
  - Time to onset of DM (defined as HbA1c ≥6.5% or as diagnosed by the investigator) in patients with pre-DM[4]

- Change from baseline in KCCQ clinical summary score[5] at Week 52
- Occurrence of all-cause hospitalisation (first and recurrent)

[1] Chronic dialysis was defined as dialysis with a frequency of twice per week or more for at least 90 days
[2] Sustained was determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (the first to last of the consecutive eGFR values)
[3] Reduction in eGFR (CKD-EPI)cr was defined as reduction in eGFR from baseline of ≥40%, eGFR <15 mL/min/1.73 m2 for patients with baseline eGFR ≥30 mL/min/1.73 m2, or eGFR <10 mL/min/1.73 m2 for patients with baseline eGFR <30 mL/min/1.73 m2
[4] Pre-DM was defined as no history of DM and no HbA1c ≥6.5% before treatment, and a pretreatment HbA1c value of ≥5.7% and <6.5%
[5] KCCQ, Kansas City cardiomyopathy questionnaire; clinical summary score measures HF symptoms (frequency and burden) and physical limitations

- Further endpoints (exploratory) include time to or occurrence of CV and/or renal events, progression or reversal of albuminuria, changes from baseline in eGFR, KCCQ scores, NYHA class, EQ-5D, NT-proBNP, albuminuria, body weight, blood pressure, pulse rate, HbA1c, FPG, etc.

Sample size

For the sample size calculation, a yearly event rate in the placebo group of 10% is assumed. The assumption is based on the CHARM-Preserved study and part of the TOPCAT study from the Americas. The annual event rates in CHARM-Preserved were 8.1% in the candesartan group and 9.1% in the placebo group. The annual rates from the Americas in the TOPCAT study were 10.4 in the spironolactone group and 12.6 in the placebo group. The trial is designed to achieve a power of 90% for a two-sided test at level $\alpha = 0.05$. The number of required events together with the number of to be randomised and treated patients were calculated assuming an accrual period of 18 months and a follow-up period of 20 months. The follow-up period was not fixed, but the trial would continue until the necessary number of events has been observed, which are confirmed by the adjudication committee. A hazard ratio of 0.8 was chosen as a conservative estimate based on the results of the EMPA-REG OUTCOME trial drop-out rate from the trial is assumed to be low (< 1% per year) and is therefore not further considered for the determination of sample size. An interim analysis was performed by the independent DMC. The EMPEROR-preserved trial included 5988 subjects (empagliflozin 10 mg: 2997 patients, placebo: 2991 patients).

Randomisation

Subjects who fulfilled all eligibility criteria were randomized double-blind in a 1:1 manner. Randomisation was performed with a permuted block design and was stratified by geographic region, diabetes status, estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area or 60 ml or more per minute per 1.73 m^2, and left ventricular ejection fraction of less than 50% or 50% or more; all measured at screening.

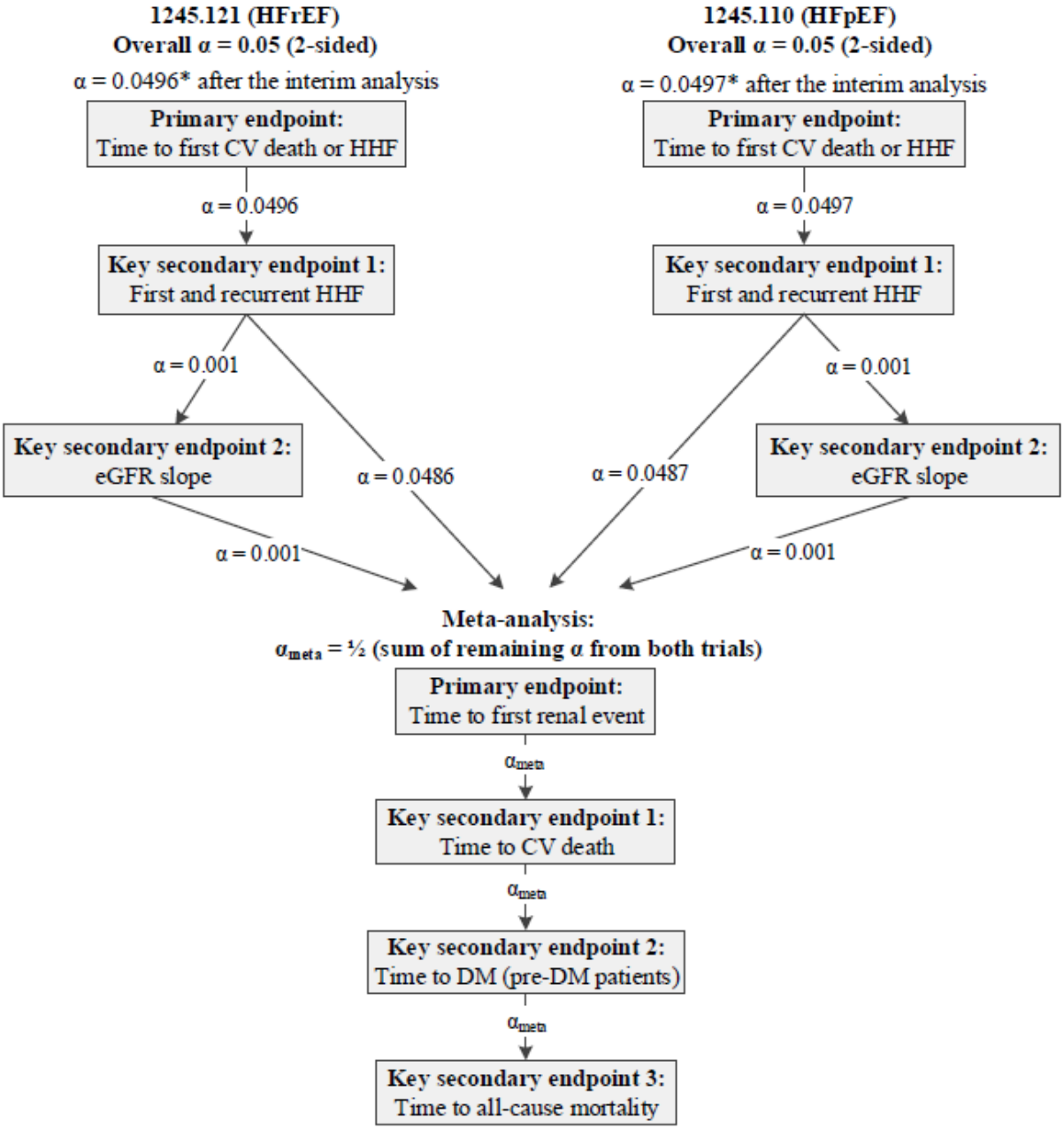
Blinding (masking)

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remain blinded with regard to the randomised treatment assignments until after database lock. The DMC is provided with unblinded data in order to allow them to review efficacy and safety and to fulfil their tasks as outlined in the data monitoring committee charter. An independent team, not otherwise involved in the conduct of the trial, provided the unblinded results to the DMC. The randomisation code is kept secret by Clinical Trial Support up to database lock.

Statistical methods

The EMPEROR-Preserved (1245.110) trial was designed to have a power of 90% for the primary endpoint at two-sided α of 0.05 to detect a hazard ratio of 0.8 between empagliflozin and placebo, which required at least 841 adjudicated primary endpoint events. After 494 events (planned approximately 500 events or about 60% of anticipated events), an interim analysis was performed by the independent DMC. Based on the interim results, the DMC recommended continuing the trial as planned. The α-level for the final analysis was 0.0497 (2-sided). A hierarchical procedure (see Figure 2) was applied to the primary and key secondary endpoints. If a confirmatory endpoint was successful (i.e. empagliflozin superior to placebo), the α would be used for the subsequent step(s). If a confirmatory endpoint was not successful, all subsequent endpoints would be evaluated in an exploratory manner. After evaluation of the first key secondary endpoint (recurrent HHF), α was to be split into 0.001 (two-sided) for the analysis of eGFR slope, and the rest transferred to an efficacy meta-analysis. If the eGFR slope analysis was successful, the α of this branch would also be transferred to the meta-analysis.

Planned hierarchical testing strategy and alpha spending for the individual trials 1245.121 and 1245.110 and the meta-analysis



Unless otherwise specified, efficacy analyses followed the ITT principle and included all randomised patients (RS; treatment assigned as randomised) and all available data up to the planned treatment discontinuation (including "off-treatment" data during unplanned treatment interruptions and after premature treatment discontinuations). Unless otherwise specified, the outcome events were based on adjudication results from the clinical event committee (CEC), according to prespecified definitions in the CEC charter.

Primary endpoint (time to adjudicated CV death or HHF)

The primary analysis was a Cox regression with factors treatment, region (Asia, Europe, Latin America, North America, and other), baseline status of DM (diabetic, pre-diabetes, and normal), age (continuous), sex, LVEF (continuous), and baseline eGFR (CKD-EPI)cr(continuous). Region, status of DM, LVEF (<50% or ≥50%), and eGFR (CKD-EPI)cr (<60 or ≥60 mL/min/1.73 m^2) at screening are randomisation stratification factors. Following the ITT principle, all data up to the end of the planned treatment period (including the data after the end of treatment for patients not completing the treatment period as planned) from all randomised patients were used. Patients without a specific endpoint event were considered censored at the last date the patient was known to be free of the event or at the end of the planned treatment period, whichever was earlier. Cumulative incidence function curves that account for competing risks (i.e. non-CV deaths) and Kaplan-Meier curves of time to censoring were displayed. The individual components that contributed to the primary endpoint were summarised descriptively. Subgroup analyses by predefined demographic and baseline characteristics (e.g. comorbidities, risk factors, and background medications) were carried out.

Key secondary endpoint 1 (adjudicated recurrent HHF)

The analysis for recurrent HHF used a joint frailty model that accounts for the dependence between recurrent HHF and CV death, with the same covariates used for the primary endpoint. All data up to the end of the planned treatment period (including the data after the end of treatment for patients not completing the treatment period as planned) from all randomised patients were used. The number of HHF events per patient was summarised descriptively. Negative binomial models were additionally fitted for recurrent HHF events. The mean cumulative incidence was displayed for adjudicated recurrent HHF. Subgroup analyses were carried out.

Key secondary endpoint 2 (eGFR slope of change from baseline)

The analysis was a random coefficient model allowing for random intercept and random slope per patient, with the same factors used for the primary endpoint and additional factors "time", "treatment-by-time interaction", and "baseline eGFR (CKD-EPI)cr-by-time interaction". Only "on-treatment" data from treated patients (i.e. measurements up to 1 day after the last intake of study medication) were used. Subgroup analyses were carried out.

Other secondary and further endpoints (exploratory)

Exploratory efficacy endpoints were analysed in the following way in general:

- Time-to-event endpoints: similar to the primary analysis of the primary endpoint. Subgroup analyses were performed for time to CV death and time to first HHF
- Recurrent events endpoints: similar to the primary analysis of the first key secondary Endpoint
- Continuous endpoints: a mixed model repeated measure (MMRM) analysis
- Categorical endpoints: descriptive

Results

Disposition of patients

This trial was a multicentre trial conducted globally (Table 4).

Table 4. Overview of screened and randomised patients by region in 1245.110 – SCR

Geographical region	Countries	Patients screened	Patients randomised
Total	23 countries	11583	5988
Europe	Poland, Czech Republic, Hungary, Germany, the Netherlands, Italy, Romania, Spain, Belgium, United Kingdom	4568	2689
Latin America	Brazil, Argentina, Colombia, Mexico	3636	1515
North America	United States, Canada	1632	719
Asia	Japan, China, Korea, Singapore	968	686
Other	South Africa, Australia, India	779	379

About half of the screened patients (48.3%) were not randomised, most commonly because of NT-proBNP levels being below protocol-specified thresholds at screening (37.6% of screened patients) (Table 5.)

Of the 5988 randomised patients, 5816 patients (97.1%) had complete follow-up for the primary endpoint and the final vital status was known for 5952 patients (99.4%); see Table 5. Of the 5985 patients treated with study medication, 1888 patients prematurely discontinued treatment (31.5%, including patients who died).

The most common reason for premature discontinuation of study medication was an AE (10.6% of patients with non-fatal events and 8.2% with fatal events). The next most common reason was refusal to continue study medication, which was balanced across the placebo (10.2%) and empagliflozin (9.5%) groups.

Table 5. Disposition of patients in 1245.110 – SCR

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Screened			11583
Randomised	2991 (100.0)	2997 (100.0)	5988 (100.0)
Final vital status known	2972 (99.4)	2980 (99.4)	5952 (99.4)
Alive	2527 (84.5)	2543 (84.9)	5070 (84.7)
Deceased	445 (14.9)	437 (14.6)	882 (14.7)
Vital status unknown	19 (0.6)	17 (0.6)	36 (0.6)
Completed trial or died[1]	2903 (97.1)	2913 (97.2)	5816 (97.1)
Prematurely discontinued trial	88 (2.9)	84 (2.8)	172 (2.9)
Consent withdrawn	25 (0.8)	27 (0.9)	52 (0.9)
Site closure[2]	15 (0.5)	8 (0.3)	23 (0.4)
Limited follow-up agreed[3]	33 (1.1)	25 (0.8)	58 (1.0)
Lost to follow-up to the primary endpoint[4]	15 (0.5)	24 (0.8)	39 (0.7)
Treated	2989 (100.0)	2996 (100.0)	5985 (100.0)
Not prematurely discontinued from trial medication	2046 (68.5)	2051 (68.5)	4097 (68.5)
Prematurely discontinued study medication	943 (31.5)	945 (31.5)	1888 (31.5)
Adverse event	553 (18.5)	575 (19.2)	1128 (18.8)
Non−fatal events	309 (10.3)	326 (10.9)	635 (10.6)
Worsening of HF	26 (0.9)	21 (0.7)	47 (0.8)
Worsening of other pre−existing disease	47 (1.6)	49 (1.6)	96 (1.6)
Other	236 (7.9)	256 (8.5)	492 (8.2)
Fatal events	244 (8.2)	249 (8.3)	493 (8.2)
Worsening of HF	57 (1.9)	36 (1.2)	93 (1.6)
Worsening of other pre−existing disease	8 (0.3)	13 (0.4)	21 (0.4)

Other	179 (6.0)	200 (6.7)	379 (6.3)
Non-compliance with protocol	30 (1.0)	24 (0.8)	54 (0.9)
Lost to follow-up	6 (0.2)	16 (0.5)	22 (0.4)
Patient refusal to continue, not due to AE	304 (10.2)	284 (9.5)	588 (9.8)
Other reason	44 (1.5)	45 (1.5)	89 (1.5)
Reason missing[5]	6 (0.2)	1 (<0.1)	7 (0.1)

[1] Patients with primary event (HHF or CV death) or follow-up for the primary endpoint until study end/death.
[2] Including patients from Site no. 1156007 (see [CTR 1245.110, c31803238, Section 9.6]) and closed sites (who did not complete the trial or die and did not withdraw consent).
[3] Patients not from a closed site who discontinued all trial activities but did not withdraw consent to vital status collection at treatment termination.
[4] Other patients with incomplete follow-up for the primary endpoint.
[5] Includes 7 patients from closed sites.

Patients who discontinued study medication prematurely were to be followed up for outcome events and vital status until the end of the trial. Vital status was known for 99.4% of the randomised patients, and 97.1% completed follow up for the primary endpoint, with balanced distribution between groups. The proportion of patients who prematurely discontinued study medication (including due to death) was balanced between the empagliflozin group and the placebo group (both 31.5%), with the most frequent reasons to discontinue study medication being adverse events (10.6% of total patients with non-fatal events and 8.2% with fatal events) and refusal to continue (9.8%).

The number of subjects that prematurely discontinued study medication was similar between empagliflozin vs placebo.

Conduct of the study

The Applicant states that the trials are carried out in compliance with the clinical trial protocol (CTP), in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH GCP, and in accordance with applicable regulatory requirements and BI's standard operating procedures.

Impact of COVID-19 pandemic on clinical visits and study medication supply

Before the onset of the COVID-19 outbreak, 5896 patients (98.5%) had been randomised in this trial, and 92 patients were randomised thereafter.

Information on the disruption due to COVID-19 to the clinical visits and study medication supply was collected on the CRF and summarised. About one-third of patients (31.8%) had at least one visit affected by COVID-19. The majority of these patients (25.7% overall) had at least one visit performed by phone instead of on-site, and 4.6% had at least one visit performed outside the protocol-defined window. A total of 1.4% of patients had an interruption of trial medication for more than 7 days due to COVID-19 and 0.8% had permanent treatment discontinuation due to COVID-19 infection.

Baseline data

Slightly more than half of the patients were men (55.3%). The majority of the patients were White (75.9%) and elderly (64.1% of patients were ≥70 years old). See Table 6. for details.

Table 6. Demographic data in 1245.110 – RS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2991 (100.0)	2997 (100.0)	5988 (100.0)
Sex, N (%)			

Male	1653 (55.3)	1659 (55.4)	3312 (55.3)
Female	1338 (44.7)	1338 (44.6)	2676 (44.7)
Race (summary), N (%)			
White	2256 (75.4)	2286 (76.3)	4542 (75.9)
Black/African American	125 (4.2)	133 (4.4)	258 (4.3)
Asian	411 (13.7)	413 (13.8)	824 (13.8)
Other including mixed race	198 (6.6)	164 (5.5)	362 (6.0)
Ethnicity, N (%)			
Not Hispanic/Latino	2236 (74.8)	2227 (74.3)	4463 (74.5)
Hispanic/Latino	754 (25.2)	770 (25.7)	1524 (25.5)
Region, N (%)			
North America	359 (12.0)	360 (12.0)	719 (12.0)
Latin America	757 (25.3)	758 (25.3)	1515 (25.3)
Europe	1343 (44.9)	1346 (44.9)	2689 (44.9)
Asia	343 (11.5)	343 (11.4)	686 (11.5)
Other	189 (6.3)	190 (6.3)	379 (6.3)
Age [years], mean (SD)	71.9 (9.6)	71.8 (9.3)	71.9 (9.4)
Age [years], N (%)			
<50	72 (2.4)	67 (2.2)	139 (2.3)
50 to <65	533 (17.8)	527 (17.6)	1060 (17.7)
65 to <75	1092 (36.5)	1122 (37.4)	2214 (37.0)
75 to <85	1088 (36.4)	1103 (36.8)	2191 (36.6)
≥85	206 (6.9)	178 (5.9)	384 (6.4)
Age [years], N (%)			
<70	1084 (36.2)	1066 (35.6)	2150 (35.9)
≥70	1907 (63.8)	1931 (64.4)	3838 (64.1)

Patients with information missing are not shown; for data, see [CTR 1245.110, c31803238, Table 15.1.4: 1]

Source data: [CTR 1245.110, c31803238, Section 10.4]

Baseline characteristics and variables

Patients with an LVEF of >40% could participate in the trial. The mean LVEF was 54.3%. About a third of patients were in each of the predefined LVEF categories (LVEF <50%, 50 to <60%, and ≥60%). Median NT-proBNP was 974 pg/mL (Q1, Q3 499, 1731). The majority of patients had SBP <140 mmHg and DBP <90 mmHg. eGFR <60 mL/min/1.73 m2 was reported for 49.9% of patients, with eGFR <30 mL/min/1.73 m2 reported for 309 patients (5.2%). Normal UACR was reported for 58.0% of patients, while 31.1% had microalbuminuria and 10.5% had macroalbuminuria. A history of atrial fibrillation or atrial flutter was reported for 52.4% of patients. Half of the patients were reported with type 2 diabetes, and 10 patients (0.2%) were reported with type 1 diabetes (Table 7.).

Table 7. Baseline characteristics in 1245.110 – RS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2991 (100.0)	2997 (100.0)	5988 (100.0)
LVEF [%], mean (SD)	54.3 (8.8)	54.3 (8.8)	54.3 (8.8)
<50%, N (%)	988 (33.0)	995 (33.2)	1983 (33.1)
50 to <60%, N (%)	1030 (34.4)	1028 (34.3)	2058 (34.4)
≥60%, N (%)	973 (32.5)	974 (32.5)	1947 (32.5)
NT-proBNP [pg/mL]			
All patients, median (Q1, Q3)	946 (498, 1725)	994 (501, 1740)	974 (499, 1731)

Patients with no atrial fibrillation or flutter from baseline ECG, N	1966	1924	3890
Median (Q1, Q3)	643 (386, 1212)	654 (380, 1197)	649 (382, 1200)
Patients with atrial fibrillation or flutter from baseline ECG, N	1016	1064	2080
Median (Q1, Q3)	1582 (1132, 2366)	1611 (1135, 2312)	1603 (1134, 2339)
Blood pressure			
SBP [mmHg], mean (SD)	131.9 (15.7)	131.8 (15.6)	131.8 (15.6)
DBP [mmHg], mean (SD)	75.7 (10.5)	75.7 (10.6)	75.7 (10.6)
SBP <140 mmHg and DBP <90 mmHg, N (%)	1917 (64.1)	1909 (63.7)	3826 (63.9)
SBP ≥140 mmHg or DBP ≥90 mmHg, N (%)	1074 (35.9)	1088 (36.3)	2162 (36.1)
Heart rate [bpm], mean (SD)	70.3 (11.8)	70.4 (12.0)	70.4 (11.9)
BMI [kg/m^2], mean (SD)	29.90 (5.92)	29.77 (5.81)	29.84 (5.87)
<30 kg/m^2, N (%)	1642 (54.9)	1654 (55.2)	3296 (55.0)
≥30 kg/m^2, N (%)	1349 (45.1)	1343 (44.8)	2692 (45.0)
eGFR (CKD-EPI) [mL/min/1.73 m^2], mean (SD)	60.6 (19.9)	60.6 (19.8)	60.6 (19.8)
≥60, N (%)	1505 (50.3)	1493 (49.8)	2998 (50.1)
≥90	237 (7.9)	231 (7.7)	468 (7.8)
60 to <90	1268 (42.4)	1262 (42.1)	2530 (42.3)
<60, N (%)	1484 (49.6)	1504 (50.2)	2988 (49.9)
45 to <60	773 (25.8)	792 (26.4)	1565 (26.1)
30 to <45	550 (18.4)	564 (18.8)	1114 (18.6)
<30, N (%)	161 (5.4)	148 (4.9)	309 (5.2)
20 to <30	152 (5.1)	142 (4.7)	294 (4.9)
<20	9 (0.3)	6 (0.2)	15 (0.3)
UACR [mg/g], N (%)			
Normal (<30)	1747 (58.4)	1727 (57.6)	3474 (58.0)
Microalbuminuria (30 to ≤300)	921 (30.8)	939 (31.3)	1860 (31.1)
Macroalbuminuria (>300)	311 (10.4)	318 (10.6)	629 (10.5)
Patients with a history of atrial fibrillation or flutter[1], , N (%)	1559 (52.1)	1576 (52.6)	3135 (52.4)
Investigator-reported medical history			
Atrial fibrillation, N (%)	1510 (50.5)	1543 (51.5)	3053 (51.0)
Atrial flutter, N (%)	200 (6.7)	206 (6.9)	406 (6.8)
Baseline ECG, N (%)	1016 (34.0)	1064 (35.5)	2080 (34.7)
Atrial flutter, N (%)	41 (1.4)	54 (1.8)	95 (1.6)
Atrial fibrillation, N (%)	986 (33.0)	1033 (34.5)	2019 (33.7)
Patients with history of atrial fibrillation[1] , N (%)	1514 (50.6)	1543 (51.5)	3057 (51.1)
Diabetes status, N (%)			
Without diabetes, N (%)	1519 (50.8)	1531 (51.1)	3050 (50.9)
Without diabetes or pre-diabetes, N (%)	540 (18.1)	530 (17.7)	1070 (17.9)
With pre-diabetes[2], N (%)	979 (32.7)	1001 (33.4)	1980 (33.1)
With diabetes, N (%)	1472 (49.2)	1466 (48.9)	2938 (49.1)
T2DM[3], N (%)	1467 (49.0)	1461 (48.7)	2928 (48.9)
Investigator-reported medical history, N (%)	1329 (44.4)	1322 (44.1)	2651 (44.3)
Previously undiagnosed diabetes, N (%)	138 (4.6)	139 (4.6)	277 (4.6)
T1DM[4], N (%)	5 (0.2)	5 (0.2)	10 (0.2)
HbA_{1c} [%], mean (SD)	7.27 (1.52)	7.24 (1.47)	7.26 (1.50)

Patients with missing information are not shown; refer to [CTR 1245.110, c31803238, Tables 15.1.4: 2 and 4 to 8] for these data.

[1] Investigator-reported medical history or baseline ECG finding
[2] Including patients with no investigator-reported medical history of diabetes and pretreatment HbA_{1c} ≥5.7% and <6.5%, or patients stratified to the group of pre-diabetes via IRT and pretreatment HbA_{1c} <6.5% (if available), or patients stratified to the group of no diabetes via IRT and pretreatment HbA_{1c} ≥5.7% and <6.5%
[3] Patients without T1DM and with investigator-reported medical history of diabetes or patients with previously undiagnosed diabetes (pretreatment HbA_{1c} ≥6.5%)
[4] Patients with investigator-reported medical history of diabetes and the type was T1DM
Source data: [CTR 1245.110, c31803238, Section 10.4]

Heart failure-related medical history

To qualify for this trial, patients had to have chronic HF with preserved ejection fraction as defined in the inclusion criteria of the trial protocol.

Most patients were in NYHA class II (81.5%). About 30% of patients had been diagnosed with HF more than 5 years before the trial. The cause of HF was ischaemic for 35.4% of patients and hypertensive for 36.5% of patients. With regard to conditions met for inclusion into the trial, the majority of patients (77.1%) had structural heart disease only, 6.4% of patients had HHF within 12 months of screening only, and 16.4% of patients met both of these conditions (Table 8.).

Table 8. Heart failure-related medical history in 1245.110 – RS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2991 (100.0)	2997 (100.0)	5988 (100.0)
NYHA class at baseline, N (%)			
I	1 (<0.1)	3 (0.1)	4 (0.1)
II	2451 (81.9)	2432 (81.1)	4883 (81.5)
III	531 (17.8)	552 (18.4)	1083 (18.1)
IV	8 (0.3)	10 (0.3)	18 (0.3)
Time since diagnosis of HF [years], mean (SD)	4.3 (5.0)	4.5 (5.2)	4.4 (5.1)
≤1, N (%)	782 (26.1)	730 (24.4)	1512 (25.3)
>1 to 5, N (%)	1325 (44.3)	1368 (45.6)	2693 (45.0)
>5 to 10, N (%)	553 (18.5)	550 (18.4)	1103 (18.4)
>10, N (%)	331 (11.1)	349 (11.6)	680 (11.4)
Cause of HF, N (%)			
Ischaemic	1038 (34.7)	1079 (36.0)	2117 (35.4)
Hypertensive	1120 (37.4)	1066 (35.6)	2186 (36.5)
Valvular heart disease	168 (5.6)	187 (6.2)	355 (5.9)
Diabetic	58 (1.9)	67 (2.2)	125 (2.1)
Alcoholism	7 (0.2)	6 (0.2)	13 (0.2)
Idiopathic	262 (8.8)	289 (9.6)	551 (9.2)
Other	338 (11.3)	302 (10.1)	640 (10.7)
HHF within 12 months before screening and/or structural heart disease[1], N (%)			
HHF within 12 months before screening only	187 (6.3)	199 (6.6)	386 (6.4)
Structural heart disease only	2317 (77.5)	2297 (76.6)	4614 (77.1)
Both	482 (16.1)	499 (16.6)	981 (16.4)

Patients with information missing are not shown; refer to [CTR 1245.110, c31803238,Tables 15.1.4: 3 and 4] for these data.
[1] Evidence of HF as defined in inclusion criterion 6
Source data: [CTR 1245.110, c31803238, Section 10.4]

Concomitant therapies

Concomitant therapies at baseline

A total of 78.6% of patients used ACE inhibitors/ARBs at baseline, and 2.2% used ARNi, 86.3% used beta-blockers, and 86.2% used diuretics, including 37.5% who used MRAs and 67.7% who used loop or high ceiling diuretics (Table 9.).

Table 9. Patients taking drugs used in heart failure, other anti-hypertensives, lipid-lowering drugs, or anti-thrombotic drugs at baseline in 1245.110 – RS

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Number of patients	2991 (100.0)	2997 (100.0)	5988 (100.0)
Drugs used in heart failure	2972 (99.4)	2985 (99.6)	5957 (99.5)
ACE inhibitors/ARBs/ARNi	2404 (80.4)	2428 (81.0)	4832 (80.7)
ACE inhibitors/ARBs	2338 (78.2)	2367 (79.0)	4705 (78.6)
ARNi	69 (2.3)	65 (2.2)	134 (2.2)
Beta-blockers	2569 (85.9)	2598 (86.7)	5167 (86.3)
Diuretics	2600 (86.9)	2563 (85.5)	5163 (86.2)
Mineralocorticoid receptor antagonists (MRAs)	1125 (37.6)	1119 (37.3)	2244 (37.5)
Loop or high ceiling diuretics	2024 (67.7)	2030 (67.7)	4054 (67.7)
Ivabradine	31 (1.0)	40 (1.3)	71 (1.2)
Cardiac glycosides	263 (8.8)	293 (9.8)	556 (9.3)
Nitrates	338 (11.3)	408 (13.6)	746 (12.5)
Hydralazine	74 (2.5)	82 (2.7)	156 (2.6)
Other anti-hypertensives	883 (29.5)	943 (31.5)	1826 (30.5)
Lipid-lowering drugs	2139 (71.5)	2103 (70.2)	4242 (70.8)
Anti-thrombotic drugs	2609 (87.2)	2631 (87.8)	5240 (87.5)

ARB: excluding valsartan when taken with sacubitril, because sacubitril/valsartan is shown as ARNi.

Source data: [CTR 1245.110, c31803238, Section 10.4]

Concomitant therapies during the trial

Concomitant therapies at baseline or any time up to the end of the planned treatment period were balanced across the treatment groups (Table 10.).

Table 10. Patients taking drugs used in heart failure, other anti-hypertensives, lipid-lowering drugs, or anti-thrombotic drugs at baseline or any time up to the end of the planned treatment period in 1245.110 – RS

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Number of patients	2991 (100.0)	2997 (100.0)	5988 (100.0)
Drugs used in heart failure	2984 (99.8)	2994 (99.9)	5978 (99.8)
ACE inhibitors/ARBs/ARNi	2535 (84.8)	2539 (84.7)	5074 (84.7)
ACE inhibitors/ARBs	2467 (82.5)	2481 (82.8)	4948 (82.6)
ARNi	148 (4.9)	116 (3.9)	264 (4.4)
Beta-blockers	2661 (89.0)	2686 (89.6)	5347 (89.3)
Diuretics	2746 (91.8)	2703 (90.2)	5449 (91.0)
MRAs	1395 (46.6)	1360 (45.4)	2755 (46.0)
Loop or high ceiling diuretics	2293 (76.7)	2227 (74.3)	4520 (75.5)
Ivabradine	52 (1.7)	51 (1.7)	103 (1.7)
Cardiac glycosides	361 (12.1)	377 (12.6)	738 (12.3)
Nitrates	536 (17.9)	548 (18.3)	1084 (18.1)
Hydralazine	129 (4.3)	131 (4.4)	260 (4.3)

Other anti-hypertensives	1142 (38.2)	1136 (37.9)	2278 (38.0)
Lipid-lowering drugs	2268 (75.8)	2232 (74.5)	4500 (75.2)
Anti-thrombotic drugs	2710 (90.6)	2728 (91.0)	5438 (90.8)

ARB: excluding valsartan when taken with sacubitril, because sacubitril/valsartan is shown as ARNi.

Source data: [CTR 1245.110, c31803238, Section 10.4]

Intensification of diuretic therapy after baseline was less frequent in the empagliflozin group vs placebo (16.1 vs 20.4% of patients), while a decrease of diuretic therapy was more frequent in the empagliflozin group vs placebo (14.1 vs 12.0%)

Extent of exposure

Median observation time up to the end of the planned treatment period was about 26 months in both treatment groups, with 94% of patients observed for at least 1 year (Table 11.).

Table 11. Observational period up to the end of the planned treatment period in 1245.110 – RS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2991 (100.0)	2997 (100.0)	5988 (100.0)
Observation time categories, N (%)			
≥12 weeks	2952 (98.7)	2973 (99.2)	5925 (98.9)
≥26 weeks	2899 (96.9)	2913 (97.2)	5812 (97.1)
≥52 weeks	2814 (94.1)	2816 (94.0)	5630 (94.0)
≥78 weeks	2248 (75.2)	2230 (74.4)	4478 (74.8)
≥104 weeks	1673 (55.9)	1663 (55.5)	3336 (55.7)
≥156 weeks	405 (13.5)	403 (13.4)	808 (13.5)
Observation time [month]			
Median (Q1, Q3)	26.1 (18.2, 33.0)	26.2 (18.0, 33.1)	26.2 (18.1, 33.1)
Mean (SD)	25.6 (9.3)	25.6 (9.4)	25.6 (9.3)
Total observation time [year]	6293.4	6304.8	12598.2

Source data: [CTR 1245.110, c31803238, Section 10.5]

Median exposure to study medication was the same (about 23 months) in both treatment groups, with 84% of patients treated for at least 1 year (Table 12.).

Table 12. Exposure to study medication in 1245.110 – TS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2989 (100)	2996 (100.0)	5985 (100.0)
Exposure categories, N (%)			
≥12 weeks	2830 (94.7)	2854 (95.3)	5684 (95.0)
≥26 weeks	2699 (90.3)	2726 (91.0)	5425 (90.6)
≥52 weeks	2511 (84.0)	2524 (84.2)	5035 (84.1)
≥78 weeks	1930 (64.6)	1911 (63.8)	3841 (64.2)
≥104 weeks	1389 (46.5)	1379 (46.0)	2768 (46.2)
≥156 weeks	308 (10.3)	303 (10.1)	611 (10.2)
Duration of exposure [month]			
Median (Q1, Q3)	23.3 (15.3, 31.4)	23.3 (15.4, 31.4)	23.3 (15.4, 31.4)
Mean (SD)	22.7 (10.8)	22.7 (10.7)	22.7 (10.7)
Total exposure [year]	5569.5	5595.3	11164.7

Exposure was calculated as date of last intake of study medication minus date of first intake, plus 1 day.

Source data: [CTR 1245.110, c31803238, Section 10.5]

Outcomes and estimation

Primary outcome, CV death or HHF

The primary endpoint was the time to the first event of adjudicated CV death or adjudicated hospitalisation for heart failure.

CV death or HHF occurred in a lower proportion of patients in the empagliflozin group (415 of 2997 patients, 13.8%) than in the placebo group (511 of 2991 patients, 17.1%), and the risk of CV death or HHF was significantly reduced with empagliflozin treatment compared with placebo (HR empagliflozin vs placebo 0.79; 95% CI 0.69 to 0.90, p = 0.0003; Table 13.).

Table 13. Time to the first event of adjudicated CV death or HHF, Cox regression, trial 1245.110 – RS

	Placebo	Empa 10 mg
Analysed patients, N (%)	2991 (100.0)	2997 (100.0)
Patients with event, N (%)	511 (17.1)	415 (13.8)
HHF as the first event	352 (11.8)	258 (8.6)
CV death as the first event	159 (5.3)	156 (5.2)
Both on the same day	0	1 (<0.1)
Incidence rate per 100 years at risk	8.67	6.86
Hazard ratio vs placebo (95% CI)		0.79 (0.69, 0.90)
(95.03% CI)[1]		(0.69, 0.90)
p-value		0.0003

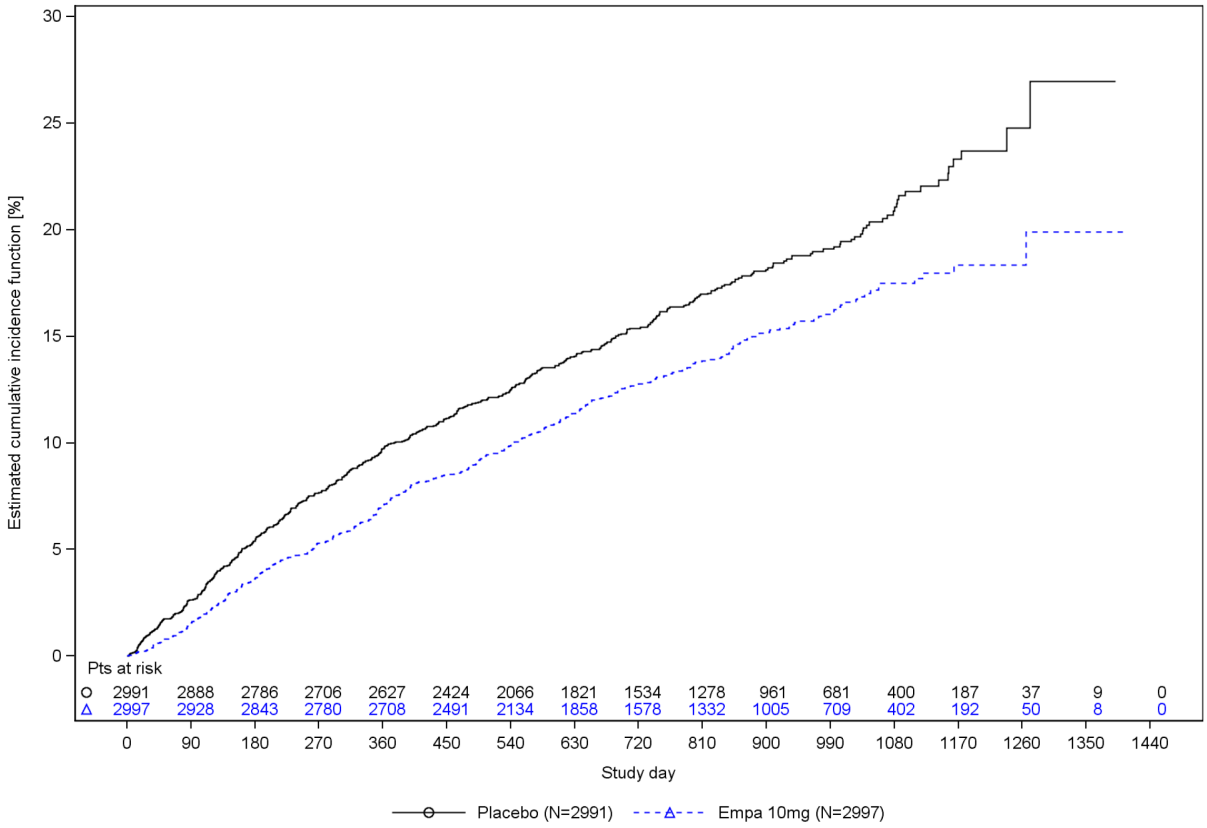
Cox regression model included factors age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment

1 Based on the reduced 2-sided α level of 0.0497 resulting from the interim analysis

Source data: [CTR 1245.110, c31803238, Section 11.1]

The separation of the estimated cumulative incidence of CV death or first HHF (considering non-CV death as a competing risk) between empagliflozin and placebo started shortly after randomisation and was maintained throughout the trial (0). The cumulative probability for censoring of patients without endpoint events was similar between treatment groups. The number of patients with a HHF or CV death during the 30 days after treatment discontinuation was similar in each treatment arm (empagliflozin: 147 patients, 5.1%; placebo: 153 patients, 5.3%).

Time to the first event of adjudicated CV death or HHF, estimated cumulative incidence function (considering non-CV death as a competing risk), trial 1245.110 – RS



Source data: [CTR 1245.110, c31803238, Section 11.1]

Key secondary outcomes, first and recurrent HHF and eGFR slope

Key secondary endpoint 1: first and recurrent HHF

The first key secondary endpoint in the hierarchical testing procedure was the occurrence of adjudicated HHF (first and recurrent).

The primary analysis consisted of a joint frailty model that accounted for the dependence between recurrent HHF and CV death and was based on all data up to the end of the planned treatment period from all randomised patients.

Adjudicated HHF occurred in fewer patients in the empagliflozin group than in the placebo group. The total number of HHF events (first and recurrent) was also lower in the empagliflozin group than in the placebo group. The risk of recurrent HHF was significantly reduced for empagliflozin versus placebo (HR 0.73, 95.03% CI 0.61 to 0.88, p = 0.0009). The hazard of recurrent HHF was positively correlated to that of CV death (indicated by a frailty exponent >0). For further information, refer to Table 14.

Table 14. Adjudicated HHF and CV death, joint frailty model, trial 1245.110 – RS

	Placebo	Empa 10 mg
Analysed patients, N (%)	2991 (100.0)	2997 (100.0)
Patients with HHF, N (%)	352 (11.8)	259 (8.6)
Patients with HHF then CV death	85 (2.8)	63 (2.1)
Patients with HHF only	267 (8.9)	196 (6.5)
Patients with CV death only, N (%)	159 (5.3)	156 (5.2)
Total number of HHF events	541	407

Hazard ratio vs placebo of recurrent HHF (95% CI)	0.73 (0.61, 0.88)
(95.03% CI)[1]	(0.61, 0.88)
p-value	0.0009
Hazard ratio vs placebo of CV death (95% CI)	0.89 (0.71, 1.12)
Frailty exponent (alpha)[2]	1.02

Joint frailty model included factors age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, treatment; variance of frailty (omega) 5.09

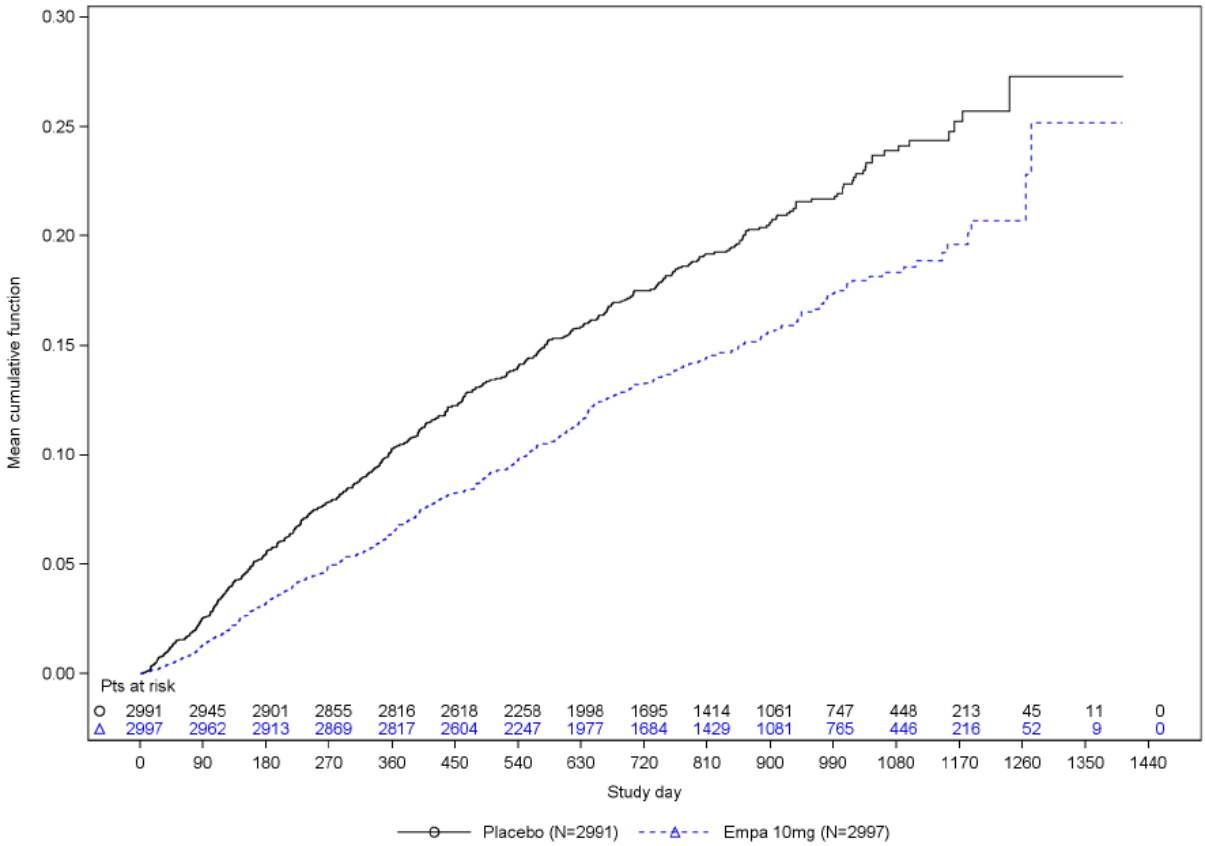
1 Based on the reduced 2-sided α level of 0.0497 resulting from the interim analysis

2 Positive correlation between the hazards for the recurrent (HHF) and terminal events (CV death) if alpha is >0

Source data: [CTR 1245.110, c31803238, Section 11.1]

The mean cumulative number of HHF events in the empagliflozin and placebo groups started to diverge shortly after randomisation and continued to separate over the course of the trial (0).

Occurrence of adjudicated HHF (first and recurrent), mean cumulative function, trial 1245.110 – RS



Source data: [CTR 1245.110, c31803238, Section 11.1]

The results of the sensitivity analyses were consistent with the results of the primary analysis for the occurrence of adjudicated HHF (first and recurrent).

Key secondary endpoint 2: eGFR slope

The second key secondary endpoint in the hierarchical testing procedure was eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline. The primary analysis was a random coefficient model allowing for random intercept and random slope per patient. Only 'on-treatment' data (based on TS and using measurements up to 1 day after the last intake of study medication) were included.

In the empagliflozin group, there was an initial dip in eGFR [mL/min/1.73 m^2] (intercept -3.016, 95% CI -3.280, -2.752). Thereafter, the estimated slope was -1.253 per year (95% CI -1.465, -1.041). In the placebo group, eGFR declined more steeply over time, with an estimated slope of -2.616 per year (95% CI -2.827, -2.405). Over the treatment period, eGFR decline in the empagliflozin group was significantly slower than in the placebo group, with an estimated difference in slope of 1.363 per year (99.9% CI 0.861, 1.865; 95% CI 1.064, 1.662; p<0.0001); see Table 15. .

Table 15. eGFR $(CKD\text{-}EPI)_{cr}$ [ml/min/1.73 m^2] slope of change from baseline, random intercept random slope model, trial 1245.110 – TS (on-treatment)

	Placebo	Empa 10 mg
Analysed patients	2911	2925
Intercept, estimate (95% CI)	−0.180 (−0.445, 0.084)	−3.016 (−3.280, −2.752)
Slope [/year], estimate (95% CI)	−2.616 (−2.827, −2.405)	−1.253 (−1.465, −1.041)
Difference vs placebo (95% CI)		1.363 (1.064, 1.662)
(99.9% CI)[1]		(0.861, 1.865)
p-value		<0.0001

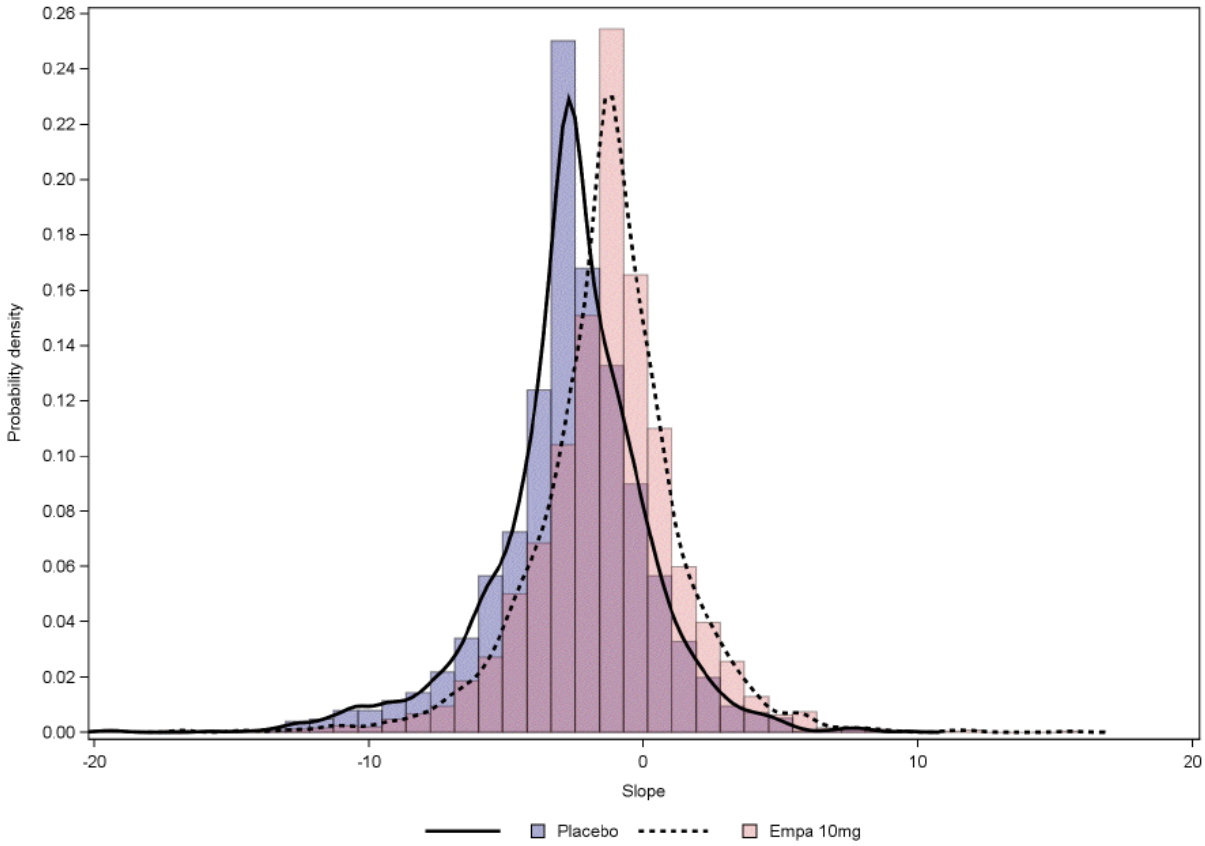
Model included factors age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, baseline eGFR (CKD-EPI)cr-by-time interaction, treatment-by-time interaction, and treatment. Intercept and slope allowed to vary randomly between patients.

1 Based on 2-sided α level of 0.001

Source data: [CTR 1245.110, c31803238, Section 11.1]

A histogram of the individual patient slopes showed a uniform shift in the empagliflozin group to slower eGFR decline compared with the placebo group, supporting that the effect of empagliflozin vs placebo treatment was observed across the population (0).

Distribution of individual patient eGFR $(CKD\text{-}EPI)_{cr}$ [mL/min/1.73 m^2] slopes of change from baseline, trial 1245.110 – TS



Source data: [CTR 1245.110, c31803238, Section 11.1]

See below for renal outcome endpoints, including sustained eGFR.

The change of eGFR slope from baseline was a key secondary endpoint and showed a slower decline in eGFR in the empagliflozin group, with an estimated difference in slope of 1.363 mL/min/1.73 m2 per year vs placebo (99.9% CI 0.861 to 1.865; p<0.0001). The Applicant also analysed change form baseline using ANCOVA, comparable to the previous application for the HFrEF indication. This will be discussed below (Secondary/Exploratory endpoints).

As discussed above, the effect on the renal composite endpoint is actually preferred for the evaluation of renal effects. Results on this endpoint will be discussed below. The effect on slope data should support the effect on the renal composite endpoint and will be evaluated in conjunction. If this confirms the overall treatment effect on GFR change, the primary analysis model can be reported in section 5.1 of the product information; however, the complete model should be presented, i.e. change in intercept and slope, to inform the prescriber on both the initial dip and subsequent change in slope.

Mortality endpoints

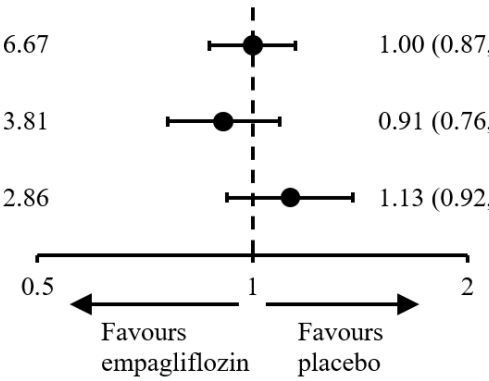
Fewer patients were reported with CV death and more patients were reported with non-CV death in the empagliflozin group than in the placebo group, and the treatment differences were not significant. The incidence of all-cause mortality was similar between treatment groups (0).

A little more than half of all deaths (55% total) were due to CV causes and most of the CV deaths were classified as sudden cardiac death (empagliflozin: 99 patients, 3.3%; placebo: 114 patients, 3.8%) and

heart failure death (empagliflozin: 40 patients, 1.3%; placebo: 51 patients, 1.7%), as expected in a population with heart failure.

Time to all-cause mortality, CV death, and non-CV death, Cox regression, trial 1245.110 – RS

	Empagliflozin 10 mg		Placebo		
	N with events	Rate/ 100 PY	N with events	Rate/ 100 PY	HR (95% CI)
All-cause mortality	422/2997 (14.1%)	6.60	427/2991 (14.3%)	6.67	1.00 (0.87, 1.15)
CV death	219/2997 (7.3%)	3.42	244/2991 (8.2%)	3.81	0.91 (0.76, 1.09)
Non-CV death	203/2997 (6.8%)	3.17	183/2991 (6.1%)	2.86	1.13 (0.92, 1.38)



Source data: [CTR 1245.110, c31803238, Section 11.1.2.4]

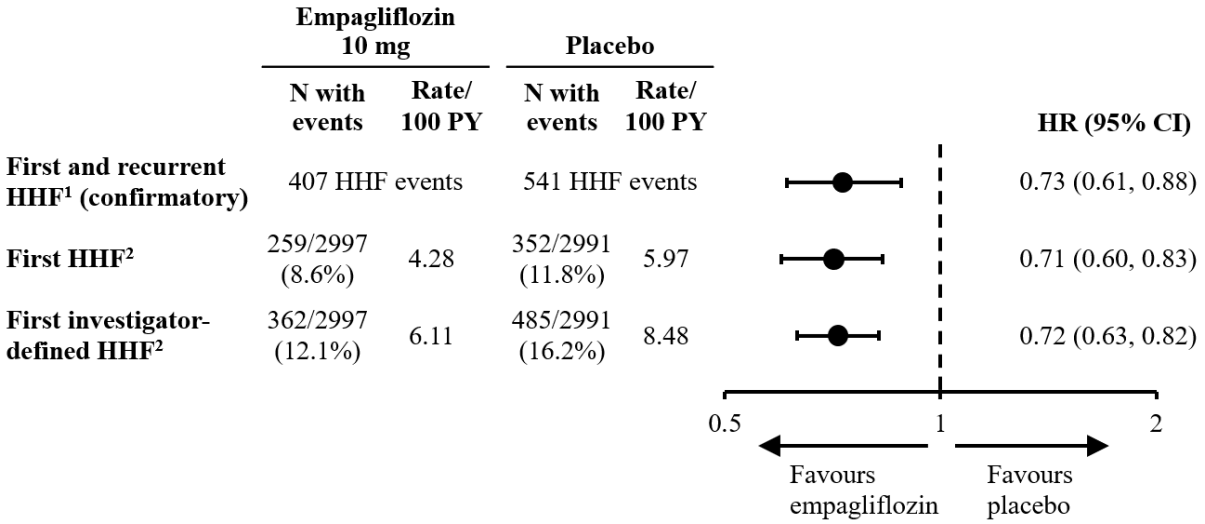
All-cause mortality was similar in both treatment groups (HR 1.00, 95%CI 0.87 – 1.15). The number of non-CV death was larger with empagliflozin, but this difference was not statistically significant (empagliflozin 203/2997, placebo 183/2991, HR 1.13, 95%CI 0.92 – 1.38). The Applicant provided an evaluation of the causes of non-CV death and could not show a specific increase in a cause of death during empagliflozin treatment.

Secondary/Exploratory endpoints

Other HHF-related endpoints

Exploratory HHF-related endpoints corroborated the treatment benefit of empagliflozin on reducing the risk of first and recurrent HHF (0).

HHF-related endpoints, trial 1245.110 – RS



1 Key secondary endpoint; joint frailty model that accounts for the dependence between occurrence of HHF and CV death

2 Cox regression, time-to-event analysis

Source data: [CTR 1245.110, c31803238, Sections 11.1.2.1 and 11.1.2.3]

The HHF results were supported by a higher win ratio for empagliflozin vs placebo (1.25, 95% CI 1.08, 1.42) when accounting for clinical hierarchies, where CV death was considered more important than HHF.

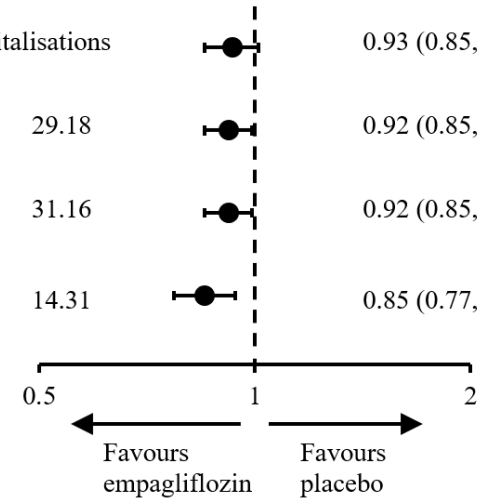
In line with the improvements in HF outcomes, there was a decrease in NT-proBNP levels in the empagliflozin group compared with placebo (adjusted gMean ratio of the relative change to baseline at Week 52 for empagliflozin vs placebo 0.95, 95% CI 0.91, 0.99).

Hospitalisation endpoints

The total number of hospitalisation events was lower with empagliflozin treatment than with placebo. Treatment with empagliflozin reduced the risk of all-cause hospitalisations based on the time to the first event (0). The treatment effect of empagliflozin started to appear after about 90 days after randomisation and was maintained throughout the trial.

Hospitalisation endpoints, trial 1245.110 – RS

	Empagliflozin 10 mg		Placebo		
	N with events	Rate/ 100 PY	N with events	Rate/ 100 PY	HR (95% CI)
First and recurrent all-cause hospitalisation[1]	2566 hospitalisations		2769 hospitalisations		0.93 (0.85, 1.01)
First all-cause hospitalisation[2]	1271/2997 (42.4%)	26.85	1340/2991 (44.8%)	29.18	0.92 (0.85, 0.99)
First all-cause mortality or all-cause hospitalisation[2]	1356/2997 (45.2%)	28.65	1431/2991 (47.8%)	31.16	0.92 (0.85, 0.99)
First investigator-defined CV hospitalisation[2]	669/2997 (22.3%)	12.15	765/2991 (25.6%)	14.31	0.85 (0.77, 0.94)



1 Joint frailty model that accounts for the dependence between occurrence of all-cause hospitalisation and all-cause mortality

2 Cox regression, time-to-event analysis

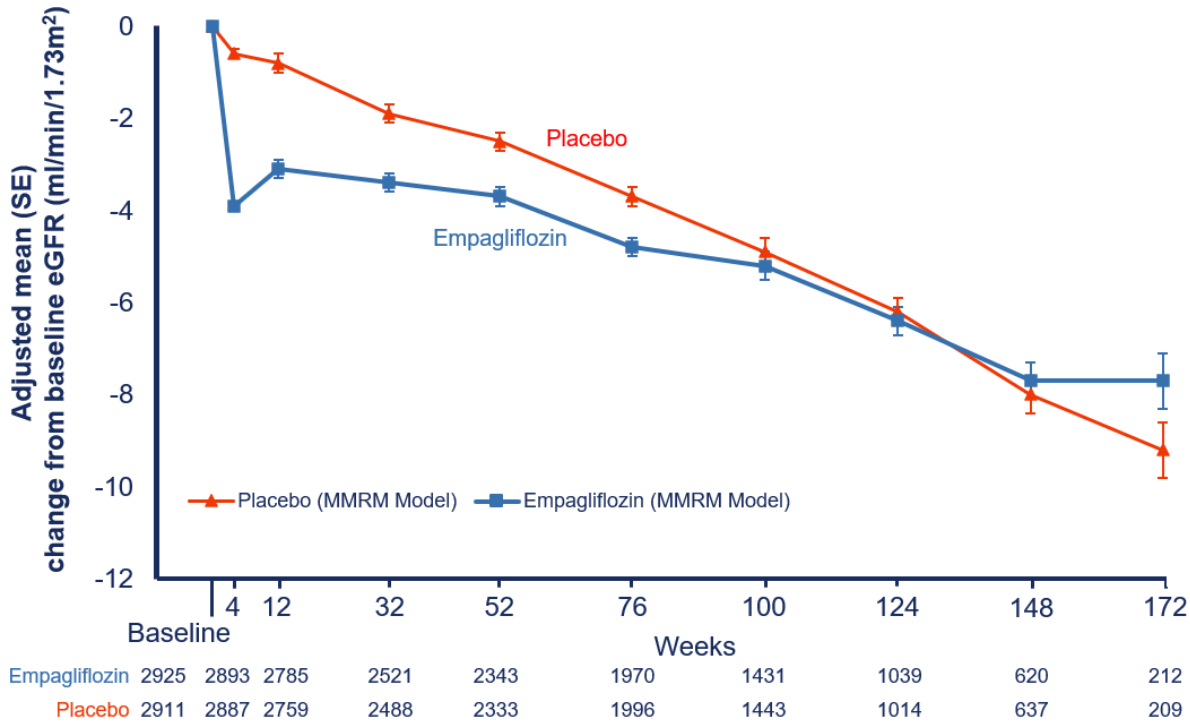
Source data: [CTR 1245.110, c31803238, Section 11.1.2.5]

Further eGFR analyses

An exploratory MMRM analysis of eGFR change from baseline including on-treatment values showed a similar trend of slowing of eGFR decline over time, consistent with the results of the slope analysis.

In the empagliflozin group, there was an initial dip in eGFR at Week 4 of about 4 mL/min/1.73 m^2. Thereafter, a slower decrease in the empagliflozin group compared with placebo was observed. Due to the initial dip, the slower decrease in eGFR in the empagliflozin group resulted in a higher mean eGFR than in the placebo group only after about 148 weeks (Figure 9).

eGFR $(CKD\text{-}EPI)_{cr}$ [mL/min/1.73 m^2] value over time MMRM results, trial 1245.110 – TS (OC-OT)



The graphical display excludes Week 196, when only 26 patients were analysed; in the underlying MMRM model, all time points were included in the analysis

Source data: [CTR 1245.110, c31803238, Section 11.1.3.7]

In an analysis of patients with valid baseline, last-value-on-treatment, and follow-up values, eGFR partially returned towards the baseline level in the empagliflozin group at the follow-up visit, about 30 days after treatment stop, while the decrease in eGFR in the placebo group persisted. The placebo-corrected eGFR change over the total study duration, i.e. from pre-treatment (baseline) to post-treatment (follow-up visit), was 2.4 mL/min/1.73 m^2 for empagliflozin (95% CI 1.6, 3.2; Table 16).

Table 16. ANCOVA results for eGFR (CKD-EPI)cr [mL/min/1.73 m^2] change from baseline to last value on-treatment and follow-up, trial 1245.110 – TS-FU

	Placebo	Empa 10 mg
Analysed patients	1608	1568
Baseline, mean (SE)	62.6 (0.5)	62.4 (0.5)
Last value on-treatment, adjusted mean (95% CI)	56.5 (56.0, 57.1)	56.1 (55.6, 56.7)
Change from baseline	-6.0 (-6.5, -5.4)	-6.4 (-6.9, -5.8)
Comparison vs placebo		-0.4 (-1.2, 0.3)
Follow-up, adjusted mean (95% CI)	56.8 (56.3, 57.4)	59.2 (58.7, 59.8)
Change from baseline	-5.7 (-6.2, -5.1)	-3.3 (-3.8, -2.7)
Comparison vs placebo		2.4 (1.6, 3.2)

Including only patients with valid baseline, last value on-treatment, and follow-up values; patients who took open-label SGLT-2 inhibitors in the follow-up period were excluded

Adjusted with a model including baseline value, age, and baseline LVEF as linear covariates, and region, baseline diabetes status, sex, and treatment as fixed effects

Source data: [CTR 1245.110, c31803238, Section 11.1.3.7]

Further renal outcomes

The composite renal endpoint (chronic dialysis, renal transplant, or sustained reduction in eGFR) occurred in similar proportions of patients in both groups. For most patients, the first recorded renal event was a sustained reduction in eGFR from a baseline of ≥40% (Table 17.).

Table 17. Time to the first event of the composite renal endpoint, Cox regression, trial 1245.110 – RS

	Placebo	Empa 10 mg
Analysed patients, N (%)	2991 (100.0)	2997 (100.0)
Patients with the composite renal endpoint, N (%)	112 (3.7)	108 (3.6)
Only sustained eGFR reduction ≥40% as the first event	102 (3.4)	95 (3.2)
Chronic dialysis as the first event	8 (0.3)	10 (0.3)
Sustained eGFR reduction ≥40% and sustained eGFR <15 mL/min/1.73 m^2 (baseline ≥30) or <10 mL/min/1.73 m^2 (baseline <30) as the first event	2 (0.1)	3 (0.1)
Incidence rate per 100 years at risk	2.23	2.13
Hazard ratio vs placebo (95% CI)		0.95 (0.73, 1.24)
Nominal p-value		0.7243

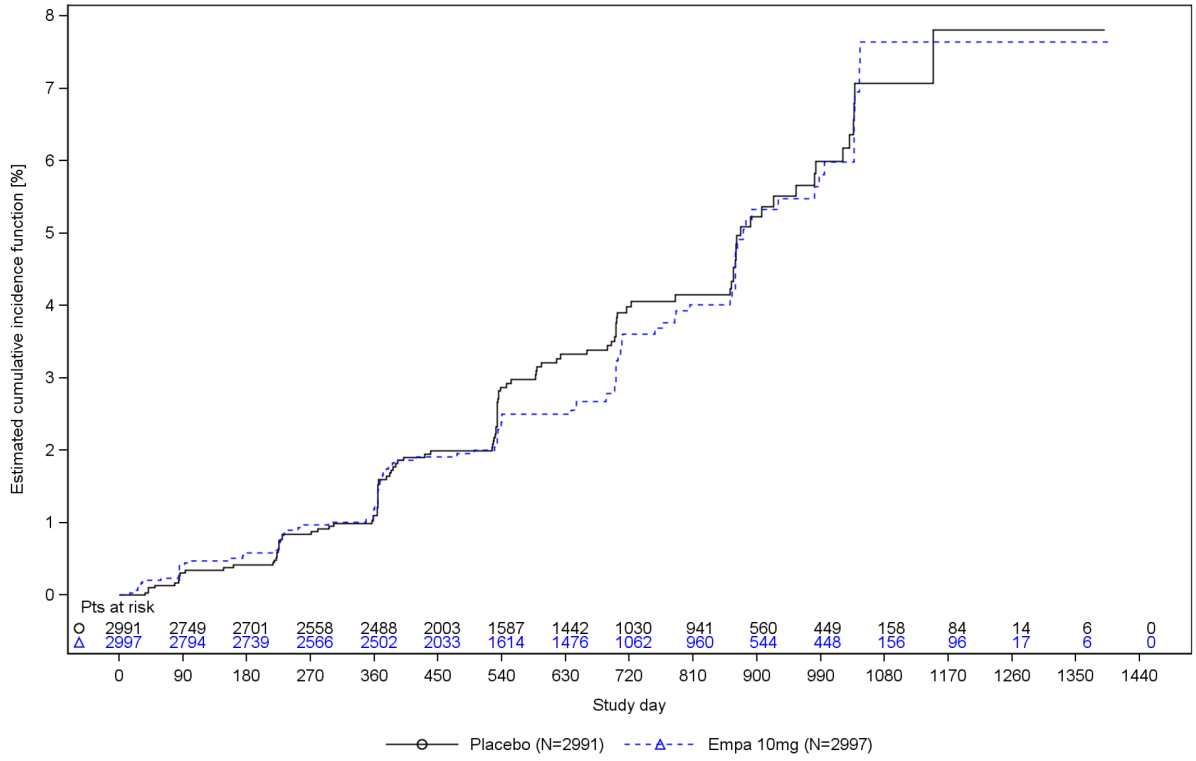
The composite renal endpoint: chronic dialysis (with a frequency of twice per week or more for at least 90 days), renal transplant, sustained reduction in eGFR from baseline of ≥40%, sustained eGFR <15 mL/min/1.73 m2 for patients with baseline eGFR ≥30 mL/min/1.73 m2, or sustained eGFR <10 mL/min/1.73 m2. For patients with baseline eGFR <30 mL/min/1.73 m2. Sustained was determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (the first to last of the consecutive eGFR values)

Cox regression model included factors age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment

Source data: [CTR 1245.110, c31803238, Section 11.1.2.6]

The estimated cumulative incidence function graph for the first event of the composite renal endpoint is shown in Figure 10. It is noted that the median follow-up for this endpoint was about 90 weeks (630 days).

Time to the first event of the composite renal endpoint, estimated cumulative incidence function (considering all-cause mortality as a competing risk), trial 1245.110 – RS



Source data: [CTR 1245.110, c31803238, Figure 15.2.3.1: 1]

Albuminuria

In this trial, 629 patients (10.5%) had macroalbuminuria (UACR >300 mg/g), 1860 patients (31.1%) had microalbuminuria (30 to ≤300 mg/g), and 3474 patients (58.0%) had normoalbuminuria (<30 mg/g) at baseline. There were improvements in the empagliflozin group versus placebo with regard to progression to or reversal of macroalbuminuria. Fewer patients in the empagliflozin group (220 of 2666 patients, 8.3%) than in the placebo group (267 of 2668 patients, 10.0%) progressed to macroalbuminuria from normo- or microalbuminuria at baseline (HR 0.82, 95% CI 0.68, to 0.98). More patients in the empagliflozin group (123 of 318 patients, 38.7%) than in the placebo group (96 of 311 patients, 30.9%) reversed from macroalbuminuria to sustained normo- or microalbuminuria (HR 1.40, 95% CI 1.06, 1.83).

An initial dip in eGFR was observed with empagliflozin treatment, followed by a slower decrease in eGFR over time. This is in line with other trials performed with SGLT2i. As described above, the key secondary renal endpoint was the eGFR slope, but the effect on slope can only be interpreted if seen in conjunction with intercept. The applicant, therefore, provided an analysis of change from baseline using ANCOVA. This resulted in a larger of similar decrease in eGFR for empagliflozin vs placebo (change from baseline: empagliflozin -6.4, placebo -6.0, comparison -0.4 (-1.2, 0.3)). But after the 30 day follow up period after treatment stop, the decrease in eGFR was smaller for the empagliflozin group (change from baseline: empagliflozin -3.3, placebo -5.7, comparison 2.4 (1.6, 3.2)), supporting that the initial dip is reversible.

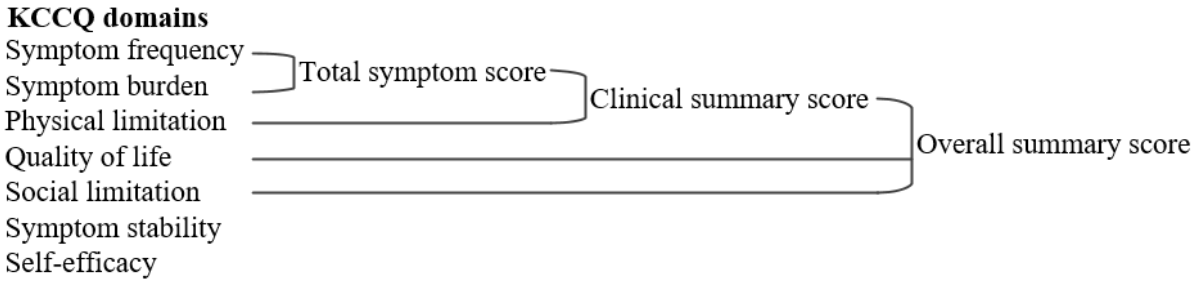
As described above, the effect on the renal composite endpoint is preferred to evaluate renal effects. The effect of empagliflozin on the eGFR slope is not supported or confirmed by the observed effects on the composite renal endpoint (i.e. chronic dialysis, renal transplant, or sustained reduction in eGFR), as the results are similar for empagliflozin vs. placebo (empagliflozin 108/2997 (3.6%), placebo 112/2991 (3.7%), HR 0.95 95%CI 0.73, 1.24). The effect on renal endpoints are therefore not robust. However, the proportion

of patients progressing to macroalbuminuria was less with empagliflozin vs. placebo, but this is also as expected from other trials with SGLT2i.

Patient-reported outcomes measured by KCCQ at Week 52

The KCCQ comprises 7 domains and 3 summary scores as shown in 0Each patient was also asked to identify the domain that was the most difficult to cope with at baseline (patient-preferred outcome). The scores of the KCCQ domains and summary scores range from 0 to 100, with higher score indicating better outcome.

KCCQ individual domains and summary scores



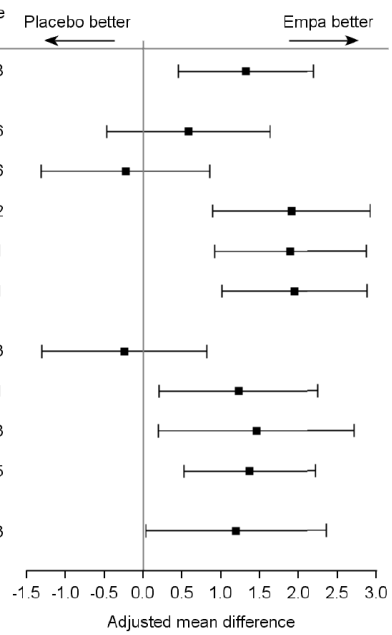
Treatment with empagliflozin improved the KCCQ clinical summary score (an exploratory secondary endpoint) from baseline to Week 52 compared with placebo (placebo-corrected adjusted mean change from baseline 1.32, 95% CI 0.45 to 2.19; 0). The score was higher at the first post-baseline assessment (Week 12) in the empagliflozin group than the placebo group, and the difference was sustained up to the last assessment (Week 52; 0 green box).

At Week 52, more patients in the empagliflozin group (1126 patients, 41.7%) than in the placebo group (1034 patients, 38.7%) showed a clinically meaningful improvement in KCCQ clinical summary score of at least 5 points from baseline (odds ratio empagliflozin vs placebo 1.120, 95% CI 0.996, 1.259). Consistently, a lower proportion of patients in the empagliflozin group (820 patients, 30.3%) than in the placebo group (906 patients, 33.9%) showed clinically meaningful deterioration of at least 5 points from baseline (odds ratio 0.852, 95% CI 0.759, 0.957).

The favourable effect of empagliflozin vs placebo in clinical summary score was mainly driven by the domains symptom frequency and symptom burden; a positive trend in favour of empagliflozin was observed for the third component domain, physical limitation. Supportive analyses of other KCCQ summary scores (overall summary score and total symptoms score) were in line with these results (Figure 12 and Figure 13).

KCCQ individual domains and summary scores change from baseline at Week 52 MMRM, trial 1245.110 – TS (on-treatment)

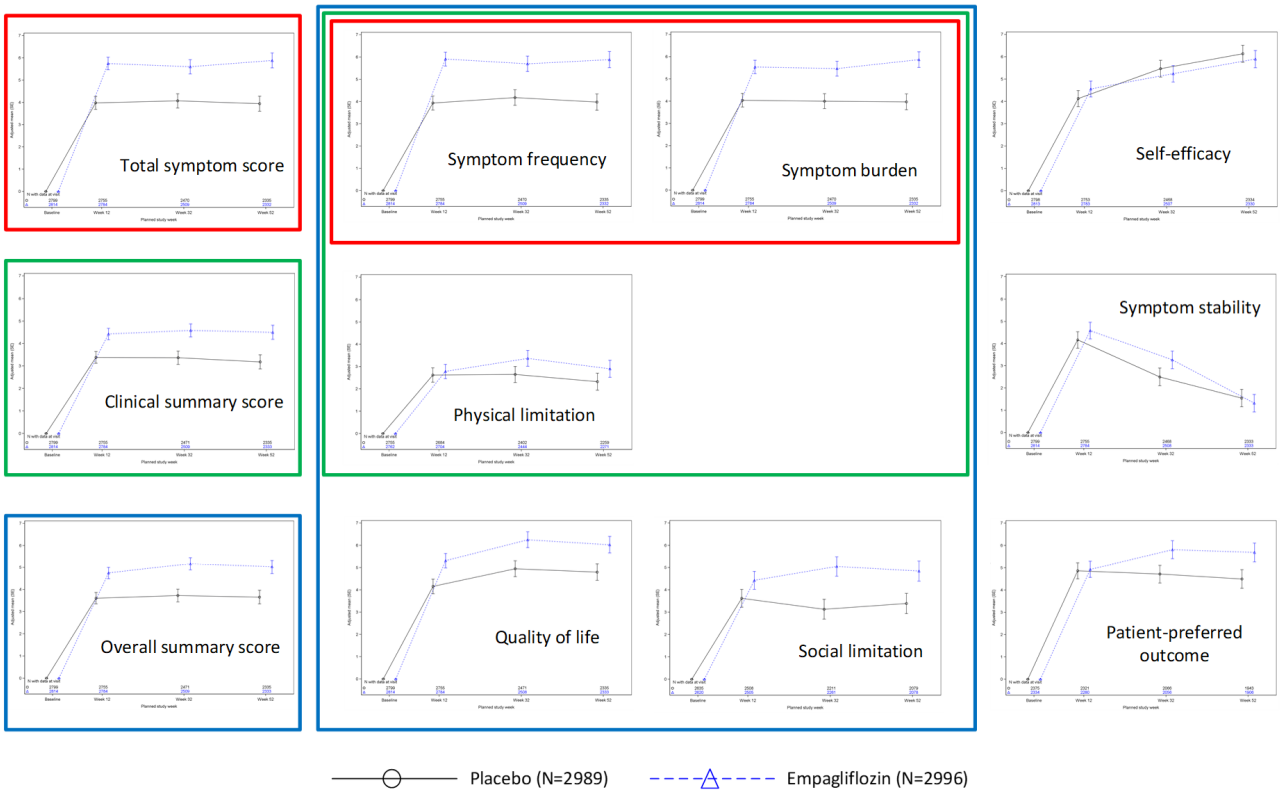
Endpoint	N analysed Empa 10mg vs	Placebo	Adjusted mean diff. (95% CI)	p-value
KCCQ clinical summary score at week 52	2814	2799	1.32 (0.45,2.19)	0.0028
KCCQ physical limitation at week 52	2762	2755	0.58 (-0.47,1.63)	0.2816
KCCQ symptom stability at week 52	2814	2799	-0.23 (-1.32,0.86)	0.6796
KCCQ symptom frequency at week 52	2814	2799	1.91 (0.89,2.93)	0.0002
KCCQ symptom burden at week 52	2814	2799	1.89 (0.92,2.87)	0.0001
KCCQ total symptom score (TSS) at week 52	2814	2799	1.94 (1.01,2.88)	<0.0001
KCCQ self efficacy at week 52	2813	2798	-0.24 (-1.30,0.82)	0.6543
KCCQ quality of life at week 52	2814	2799	1.23 (0.20,2.25)	0.0191
KCCQ social limitation at week 52	2620	2635	1.46 (0.20,2.71)	0.0233
KCCQ overall summary score at week 52	2814	2799	1.37 (0.52,2.21)	0.0015
KCCQ patient preferred outcome at week 52	2334	2375	1.19 (0.03,2.36)	0.0443



Source data: [CTR 1245.110, c31803238, Section 11.1.2.7]

The improvement in HF symptoms was in line with the HF clinical outcome results and consistent with the observed improvements in NYHA class with empagliflozin treatment. More patients in the empagliflozin group (609 patients, 22.6%) than in the placebo group (490 patients, 18.3%) improved in NYHA class from baseline to Week 52, and fewer patients in the empagliflozin group (92 patients, 3.4%) than in the placebo group (130 patients, 4.8%) worsened.

KCCQ summary scores and domains change from baseline MMRM results, trial 1245.110 – TS (on-treatment)



The summary scores were based on the domains enclosed by the matching coloured boxes, also see 0.

The change from baseline in KCCQ clinical summary score at Week 52 was a secondary/exploratory endpoint. The mean treatment difference in change was 1.32, 95% CI 0.45 to 2.19. Although statistically significant, the treatment difference appears modest, and the clinical relevance is questionable. The Applicant also provided the proportion of patients achieving a clinically relevant change (i.e. 5 points). This endpoint was not defined as a secondary endpoint but resulted in a larger proportion of patients with clinically relevant change (empagliflozin 1126 patients, 41.7%; placebo 1034 patients, 38.7%), but the difference in percentage is small. For other KCCQ scores, a treatment difference was also observed, supporting a consistent finding. Nevertheless, the treatment differences are again considered small and not clinically relevant.

Other efficacy endpoints

Diabetes-related endpoints

The onset of DM in patients with pre-DM occurred in fewer patients in the empagliflozin group (120 of 1001 patients, 12.0%) than in the placebo group (137 of 979 patients, 14.0%; HR 0.84, 95% CI 0.65, 1.07). A reduction in HbA_{1c} of about 0.2% was only seen in the empagliflozin group compared with placebo in patients with diabetes at baseline. The results for the onset of DM in patients with pre-DM and in patients without DM in the meta-analysis of the EMPEROR trials showed consistent favourable trends for empagliflozin.

Other clinical cardiovascular outcome events

The following clinical events are described in this section:

- 3-point MACE (adjudicated CV death, adjudicated non-fatal MI, or adjudicated nonfatal stroke)
- Adjudicated MI (fatal or non-fatal)
- Composite of adjudicated CV death or adjudicated non-fatal MI
- Adjudicated stroke (fatal or non-fatal)
- Composite of adjudicated CV death or adjudicated non-fatal stroke
- Adjudicated TIA
- Time to new onset of atrial fibrillation (as ECG findings or as AEs with PT "atrial fibrillation")

The results for both treatment groups were similar for all endpoints as based on Cox regression analysis and estimated cumulative incidence analysis; see Table 18.

Table 18. Time to 3-point MACE, MI, stroke, TIA, and new onset of atrial fibrillation, Cox regression, trial 1245.110 – RS

	Placebo	Empa 10 mg
Analysed patients, N (%)	2991 (100.0)	2997 (100.0)
Patients with 3-point MACE, N (%)	331 (11.1)	319 (10.6)
Incidence rate per 100 years at risk	5.38	5.17
Hazard ratio vs placebo (95% CI)		0.97 (0.83, 1.13)
Nominal p-value		0.6744
Patients with CV death or non-fatal MI, N (%)	273 (9.1)	254 (8.5)
Incidence rate per 100 years at risk	4.38	4.07
Hazard ratio vs placebo (95% CI)		0.94 (0.79, 1.11)
Nominal p-value		0.4423
Patients with MI (fatal or non-fatal), N (%)	40 (1.3)	49 (1.6)
Incidence rate per 100 years at risk	0.64	0.78
Hazard ratio vs placebo (95% CI)		1.23 (0.81, 1.86)
Nominal p-value		0.3375
Patients with CV death or non-fatal stroke, N (%)	302 (10.1)	287 (9.6)
Incidence rate per 100 years at risk	4.86	4.62
Hazard ratio vs placebo (95% CI)		0.96 (0.81, 1.12)
Nominal p-value		0.5809
Patients with stroke (fatal or non-fatal), N (%)	84 (2.8)	92 (3.1)
Ischaemic	74 (2.5)	83 (2.8)
Haemorrhagic	8 (0.3)	7 (0.2)
Unclassified	2 (0.1)	2 (0.1)
Incidence rate per 100 years at risk	1.35	1.48
Hazard ratio vs placebo (95% CI)		1.10 (0.82, 1.47)
Nominal p-value		0.5393
Patients with TIA, N (%)	27 (0.9)	20 (0.7)
Incidence rate per 100 years at risk	0.43	0.32
Hazard ratio vs placebo (95% CI)		0.74 (0.41, 1.32)
Nominal p-value		0.3050
Patients without baseline or history of Afib[1], N (%)	1477 (100.0)	1454 (100.0)
Patients with new onset of atrial fibrillation as ECG findings or as AEs, N (%)	119 (8.1)	116 (8.0)
Incidence rate per 100 years at risk	4.04	3.95
Hazard ratio vs placebo (95% CI)		1.00 (0.77, 1.29)
Nominal p-value		0.9790

Cox regression model included factors age, baseline eGFR $(CKD\text{-}EPI)_{cr}$, region, baseline diabetes status, sex, baseline LVEF, and treatment

[1] Based on investigator-reported medical history or baseline ECG

Source data: [CTR 1245.110, c31803238, Section 11.1]

NYHA class change from baseline

More patients in the empagliflozin group (609 patients, 22.6%) than in the placebo group (490 patients, 18.3%) had an improved NYHA class at Week 52 compared with baseline, and fewer patients in the empagliflozin group (92 patients, 3.4%) than in the placebo group (130 patients, 4.8%) had a worsened NYHA class.

Body weight change from baseline

There was a small decrease in body weight in the empagliflozin group, with a placebo-corrected adjusted mean change at Week 52 from baseline of -1.28 kg (95% CI -1.54, -1.03).

Blood pressure change from baseline

There was no marked change in blood pressure in the empagliflozin group, with a placebo-corrected adjusted mean change at Week 52 from baseline of -1.2 mmHg (95% CI -2.1, -0.3) for SBP and -0.2 mmHg (95% CI -0.7, 0.3) for DBP.

The effects of empagliflozin were accompanied by effects on body weight, improvement in NYHA classification and reduction in systolic blood pressure. This is in line with previous observations with SGLT2i treatment. The HR > 1 for myocardial infarction and strokes will be discussed in the safety section.

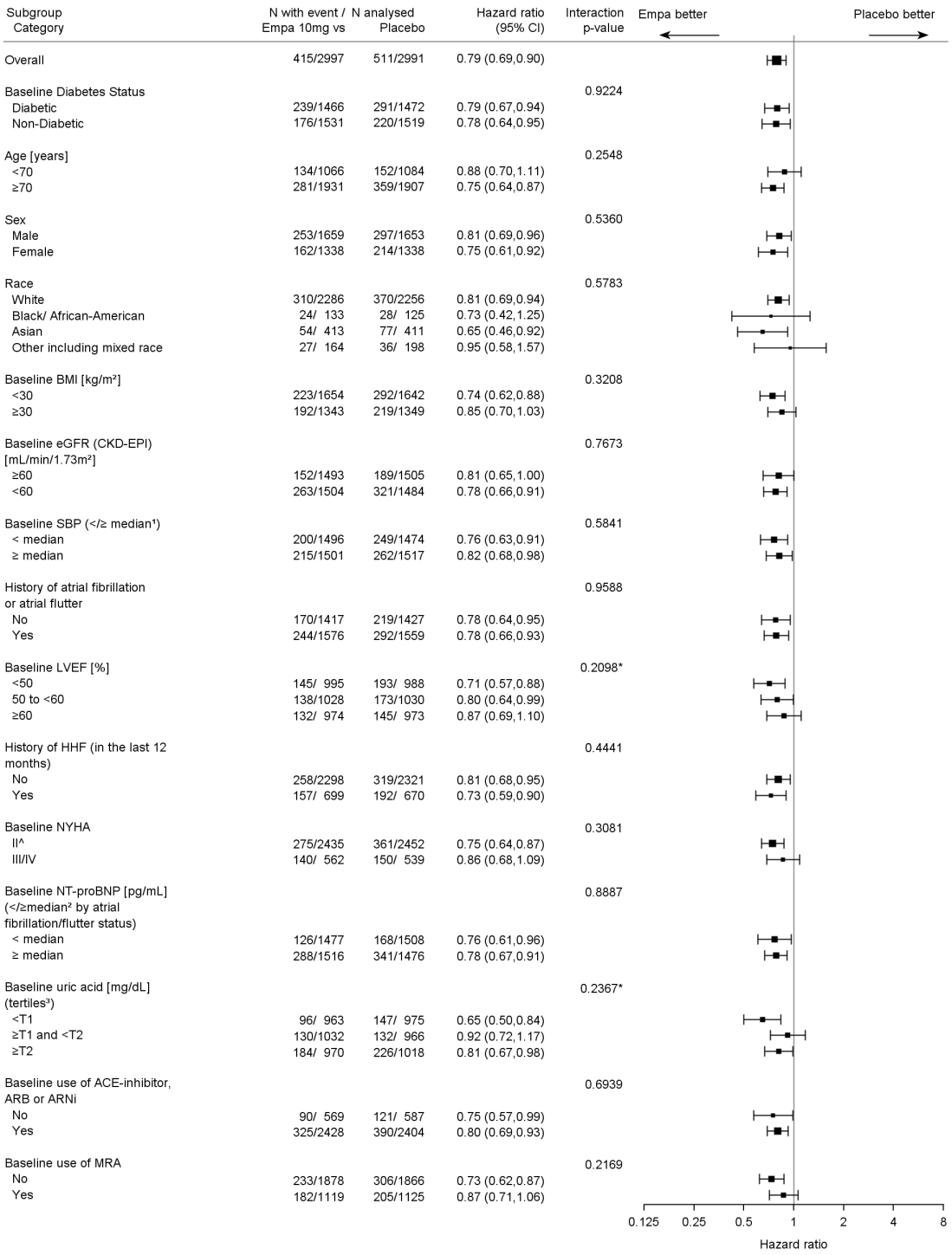
Ancillary analyses

Subgroup analyses

Primary endpoint: CV death or HHF

The consistency of the treatment effect was investigated in predefined subgroups by demographics, baseline characteristics, and baseline medications. The results were consistent across the subgroups, with the interaction p-values above 0.05 for all analysed subgroups, including diabetes status and LVEF (0 and 0). Note that the subgroup analyses were not adjusted for multiple testing and that effects observed in small subgroups are more prone to random variation. Age (interaction p-value = 0.5162), eGFR (interaction p-value = 0.6331), or LVEF (interaction p-value = 0.4333) analysed as a continuous variable had no relevant impact on the results of the primary analysis. (Figure 14, 15 and 16)

Subgroup analyses for the time to the first event of adjudicated CV death or HHF, Cox regression, trial 1245.110 – RS



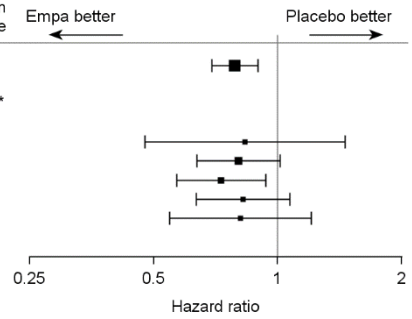
Interaction p-values are nominal. The subgroup analyses were not adjusted for multiple testing.

* Trend test. Other footnotes are explained in [CTR 1245.110, c31803238, Figure 15.2.1.3: 1].

Source data: [CTR 1245.110, c31803238, Section 11.1]

Subgroup analysis for the time to the first event of adjudicated CV death or HHF by baseline eGFR (5 categories), Cox regression, trial 1245.110 – RS

Subgroup Category	N with event / Empa 10mg vs	N analysed Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	415/2997	511/2991	0.79 (0.69,0.90)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]				0.9406*
≥90	22/ 231	28/ 237	0.83 (0.48,1.46)	
60 to <90	130/1262	161/1268	0.80 (0.64,1.01)	
45 to <60	112/ 792	143/ 773	0.73 (0.57,0.93)	
30 to <45	106/ 564	123/ 550	0.82 (0.64,1.07)	
<30	45/ 148	55/ 161	0.81 (0.55,1.21)	

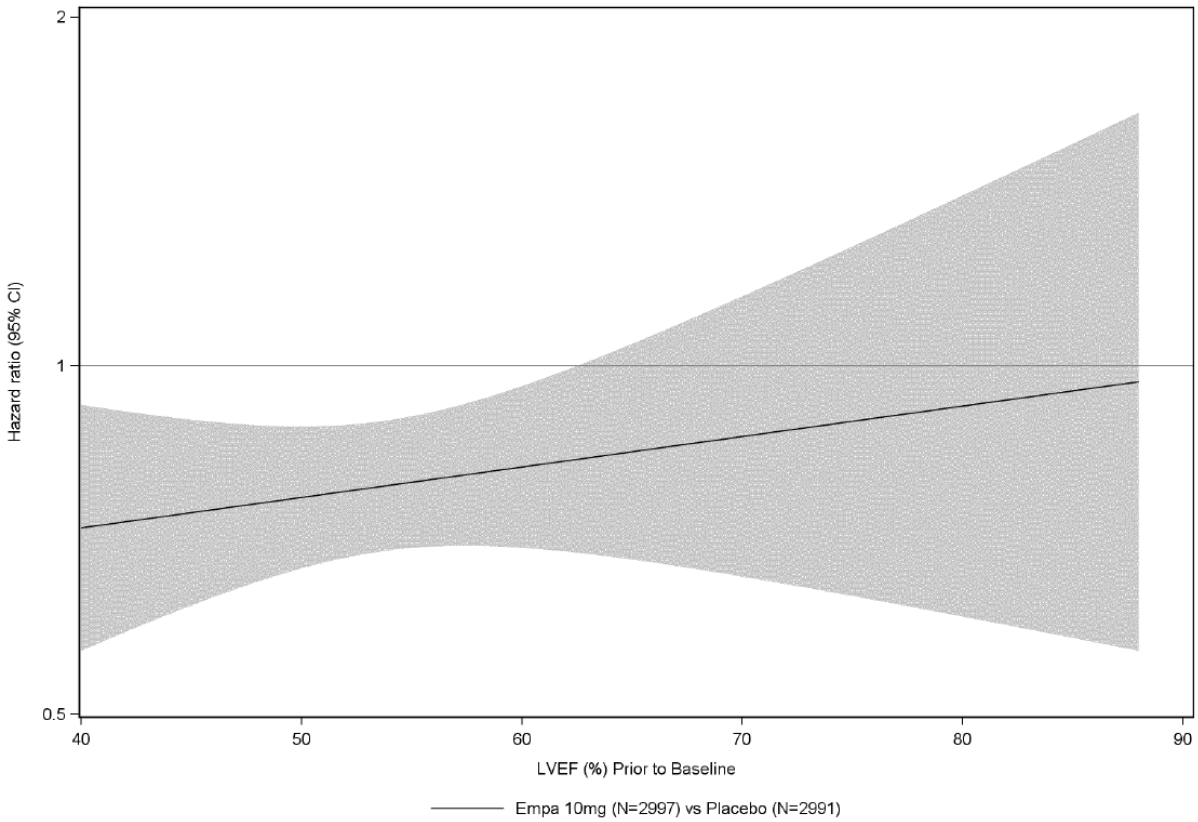


The subgroup analysis was not adjusted for multiple testing.

* Trend test nominal p-value

Source data: [CTR 1245.110, c31803238, Appendix 16.1.13.2, Figure 1.3.3]

Hazard ratio for time to first event of adjudicated HHF or CV death by baseline LVEF [%] (continuous), trial 1245.110 – RS



The treatment by LVEF p-value = 0.4333

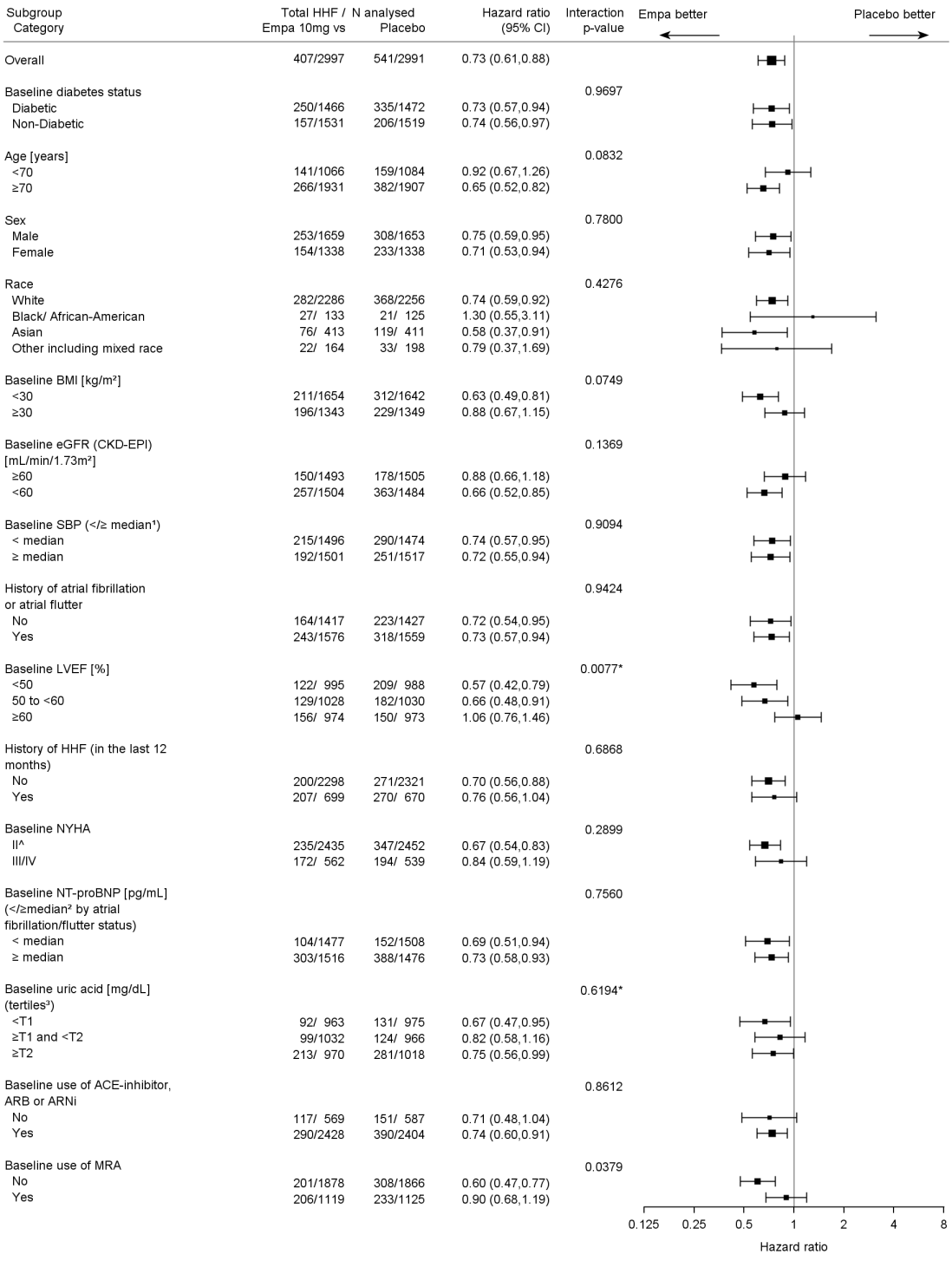
Source data: [CTR 1245.110, c31803238, Figure 15.2.1.3.3: 1]

Key secondary endpoint 1: first and recurrent HHF

In general, the subgroup analyses of first and recurrent HHF showed similar trends to those observed for the primary endpoint. Forest plots of the subgroup analyses are presented in Figure 17 and 0 Interaction p-values of <0.05 were observed in the subgroup analyses by LVEF and the use of MRAs.

Patients with LVEF <60% at baseline appeared to have a greater effect of empagliflozin versus placebo than patients with LVEF values ≥60%. When the time to first HHF was analysed (i.e. not including recurrent events), this trend was less pronounced. With regard to the use of MRAs, patients taking MRAs at baseline showed a smaller effect of empagliflozin vs placebo than patients who were not taking MRAs. However, the HR was below 1 for both subcategories, and there was considerable overlap in the confidence intervals.

Subgroup analyses for the time to the occurrence of adjudicated HHF (first and recurrent), joint frailty model, trial 1245.110 – RS



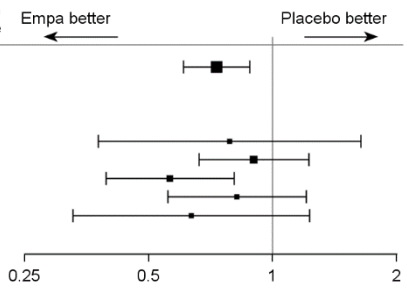
Interaction p-values are nominal. The subgroup analyses were not adjusted for multiple testing.

The footnotes are explained in [CTR 1245.110, c31803238, Figure 15.2.2.1.3: 1].

Source data: [CTR 1245.110, c31803238, Section 11.1]

Subgroup analysis for the time to the occurrence of adjudicated HHF (first and recurrent) by baseline eGFR (5 categories), joint frailty model, trial 1245.110 – RS

Subgroup Category	Total HHF / Empa 10mg vs	N analysed Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	407/2997	541/2991	0.73 (0.61,0.88)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]				0.4654*
≥90	19/ 231	31/ 237	0.79 (0.38,1.64)	
60 to <90	131/1262	147/1268	0.90 (0.66,1.22)	
45 to <60	94/ 792	157/ 773	0.56 (0.39,0.81)	
30 to <45	112/ 564	134/ 550	0.82 (0.56,1.21)	
<30	51/ 148	72/ 161	0.63 (0.33,1.23)	



The subgroup analysis was not adjusted for multiple testing.

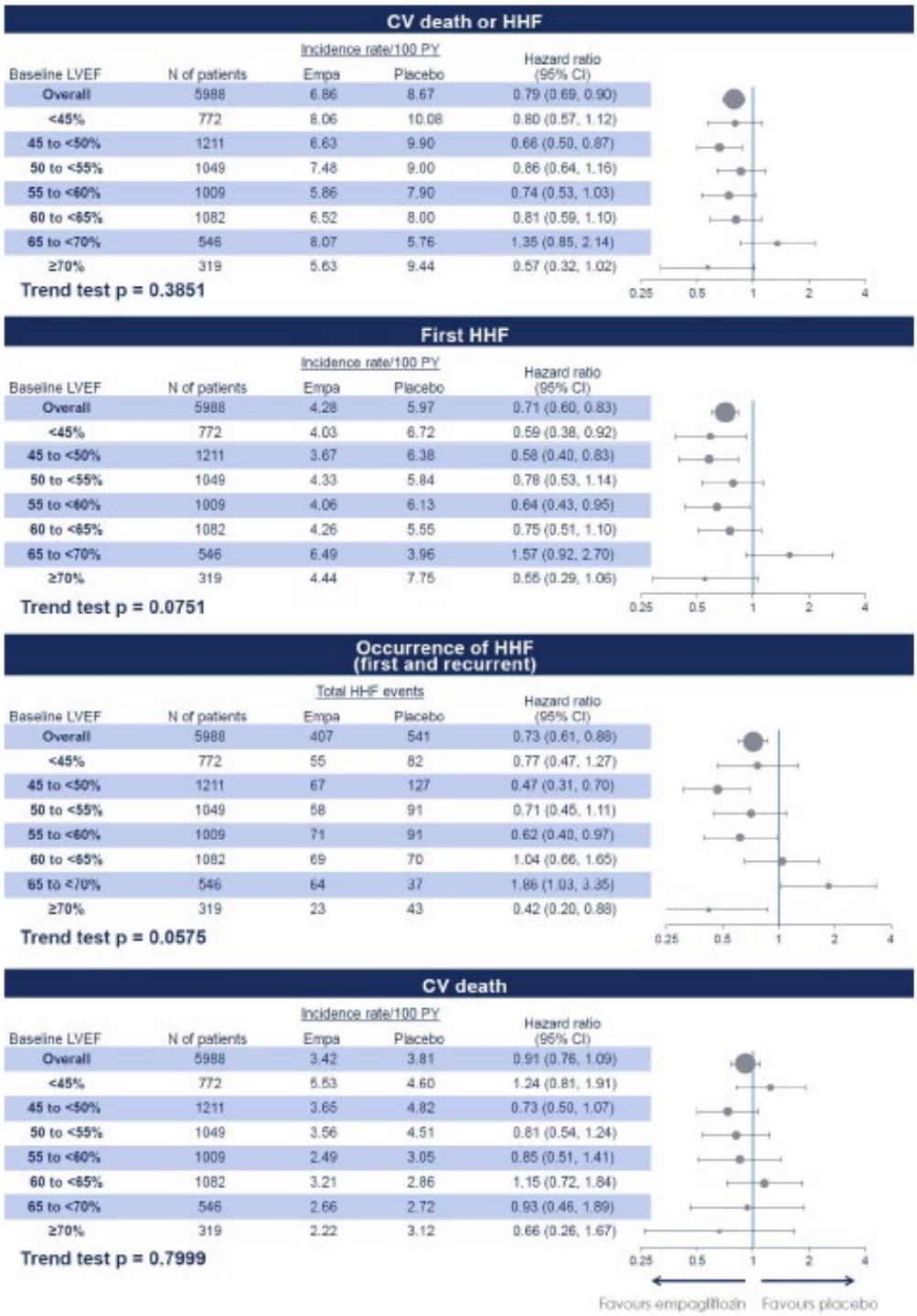
* Trend test nominal p-value

Source data: [CTR 1245.110, c31803238, Appendix 16.1.13.2, Figure 1.3.4]

Post hoc analyses of HF outcomes by LVEF

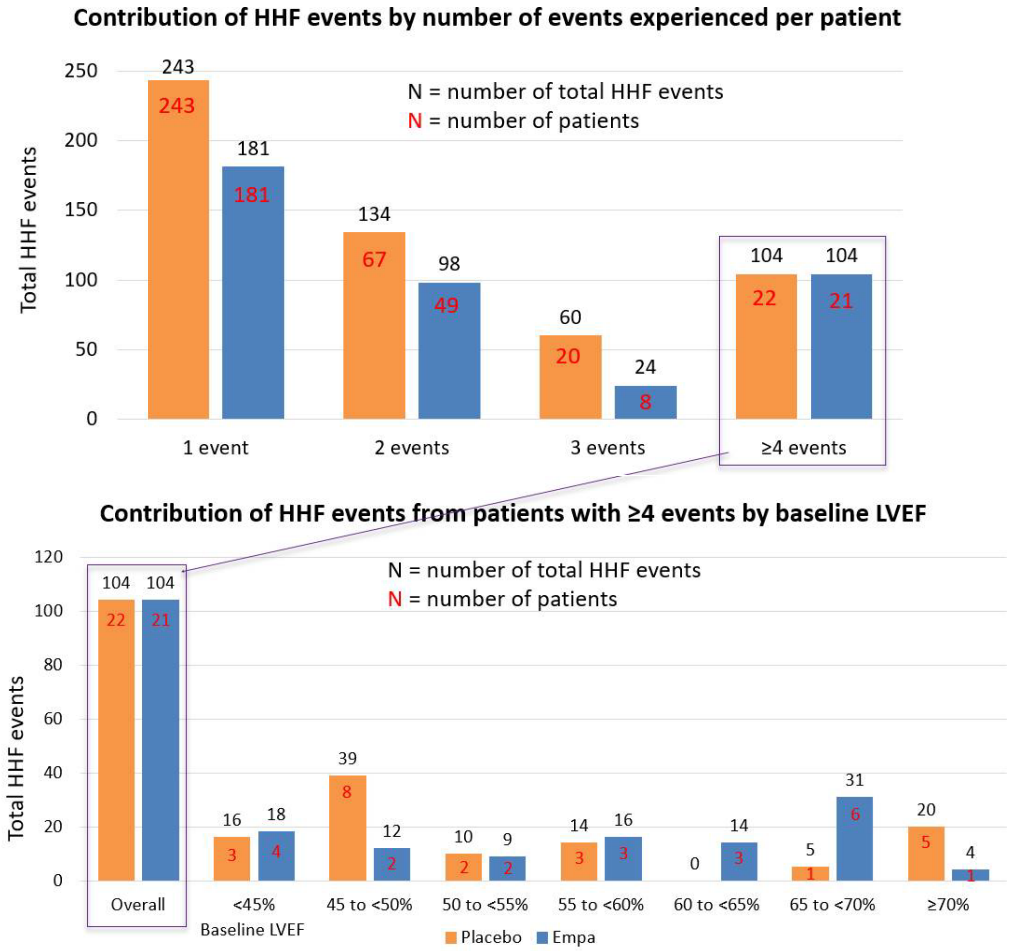
The Applicant analysed subgroups by LVEF in more detail for the HF outcomes, using a 5% increment of LVEF to categorise patients. Patients with LVEF ≥70% (N = 319; max 88%) were grouped together to avoid very small subgroups. No consistent trend by LVEF is observed for any endpoint analysed, with all trend test p-values >0.05, indicating that the results for the subgroups were consistent with the results in the overall trial population. However, only for patients with LVEF of 65 to <70%, was the HR above 1 for the first HHF and the occurrence of HHF (first and recurrent). The HR for CV death was consistent across the subgroups. As the majority of the primary endpoint events were HHF, accordingly the HR for the primary endpoint in the subgroup with LVEF of 65 to <70% for HHF or CV death was also above 1 (Figure 19). For the analysis of the first HHF, a numerically higher proportion of patients in the empagliflozin arm (33 of 263, 12.5%) than in the placebo arm (22 of 283, 7.8%) had an event in the subgroup with LVEF of 65 to <70%, while it was the opposite for all other subgroups (e.g. in the subgroup with LVEF ≥70%: 15 of 165 patients, 9.1% in the empagliflozin arm and 23 of 154 patients, 14.9% in the placebo arm had HHF). The incidence rates per 100 patient-years among the subgroups were similar within the respective treatment arm (ranging from 3.67 to 4.44 in the empagliflozin arm and 5.55 to 7.75 in the placebo arm), except in the subgroup with LVEF of 65 to <70%. In this subgroup, the incidence rate was highest (6.49) among all subgroups in the empagliflozin arm while lowest (3.96) among all subgroups in the placebo arm (Figure 19).

Subgroup analyses of HF outcomes by baseline LVEF – RS, post hoc



Overall, for patients who had HHF events, fewer in the empagliflozin arm had 1, 2, and 3 HHF events, but a similar number had 4 or more HHF events compared with placebo (Figure 20 upper part). For patients who had 4 or more events, in the subgroup of LVEF of 65 to <70%, 6 patients in the empagliflozin arm had 31 events while 1 patient in the placebo arm had 5 events, which substantially contributed to the imbalance in the analysis of the first and recurrent HHF in this subgroup (Figure 20 lower part).

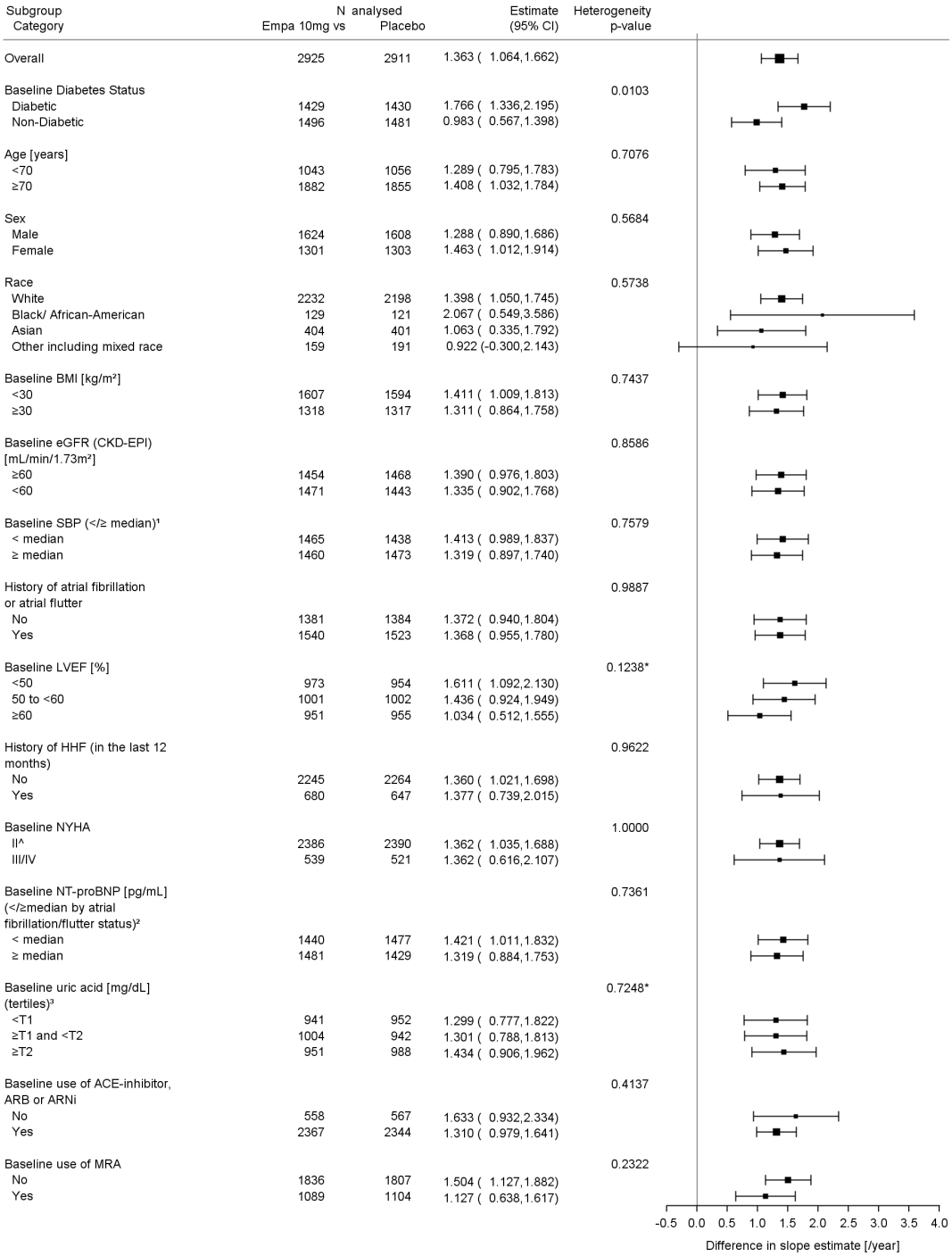
Contribution of HHF events by number of events experienced per patient (upper) and from patients with 4 or more events by baseline LVEF subgroups (lower)



Key secondary endpoint 2: eGFR slope

The results for the eGFR slope analysis were generally consistent across the predefined subgroups by demographics, baseline characteristics, and baseline medications (Figure 21. and 0). Patients with diabetes showed a larger effect of empagliflozin vs placebo than patients without diabetes. However, in both of these subgroups, the eGFR decline was slower with empagliflozin treatment than with placebo.

Subgroup analyses for eGFR (CKD-EPI)cr [mL/min/1.73 m^2] slope of change from baseline, random intercept random slope model, trial 1245.110 – TS (on-treatment)



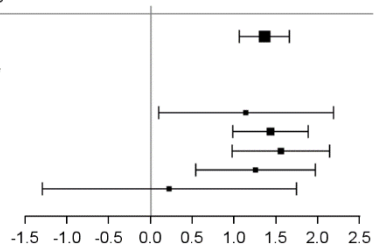
Interaction p-values are nominal. The subgroup analyses were not adjusted for multiple testing.

* Trend test. Other footnotes are explained in [CTR 1245.110, c31803238, Figure 15.2.2.2.2: 1].

Source data: [CTR 1245.110, c31803238, Section 11.1]

Subgroup analysis for eGFR $(CKD\text{-}EPI)_{cr}$ [mL/min/1.73 m^2] slope of change from baseline by baseline eGFR (5 categories), random intercept random coefficient model, trial 1245.110 – TS (on-treatment)

Subgroup Category	N analysed Empa 10mg vs	Placebo	Estimate (95% CI)	Heterogeneity p-value
Overall	2925	2911	1.363 (1.064,1.662)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]				0.4892*
≥90	229	228	1.140 (0.094,2.187)	
60 to <90	1225	1240	1.435 (0.984,1.885)	
45 to <60	776	753	1.557 (0.975,2.140)	
30 to <45	554	536	1.258 (0.541,1.974)	
<30	141	154	0.224 (-1.299,1.746)	



The subgroup analysis was not adjusted for multiple testing.

* Trend test nominal p-value

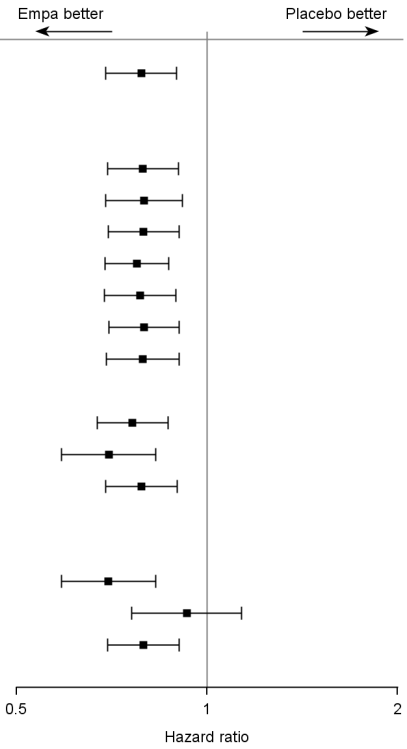
Source data: [CTR 1245.110, c31803238, Appendix 16.1.13.2, Figure 1.3.6]

Primary endpoint sensitivity analyses

The sensitivity analyses were exploratory, and the results were generally consistent with the results of the primary analysis. The treatment effect was more pronounced for the period before COVID-19 outbreak, i.e. before the dates specified in the TSAP (01 Dec 2019 for China and 01 Jan 2020 for all other countries). As shown by the sensitivity analyses including events after the end of treatment until individual trial completion, the modification of the primary analysis had no impact on the results (0).

Sensitivity analyses for the primary endpoint: time to the first event of adjudicated CV death or HHF, trial 1245.110

	N with event / N analysed Empa 10mg vs	Placebo	Hazard ratio (95% CI)
Primary endpoint	415/2997	511/2991	0.79 (0.69,0.90)
Sensitivity analyses			
Analysis repeated with no covariate adjustment - RS	415/2997	511/2991	0.79 (0.70,0.90)
Treated patients while on treatment + 30 days - TS	361/2996	439/2989	0.80 (0.69,0.91)
Multiple imputation for lost to follow-up - RS*	/2997	/2991	0.79 (0.70,0.90)
Based on investigator defined events - RS	516/2997	642/2991	0.77 (0.69,0.87)
Competing risk model by Fine-Gray - RS	415/2997	511/2991	0.78 (0.69,0.89)
Until individual trial completion - RS	431/2997	525/2991	0.79 (0.70,0.90)
Excluding events without documented physical signs/symptoms - RS	396/2997	486/2991	0.79 (0.69,0.90)
Including additional prognostic covariates - RS	415/2997	511/2991	0.76 (0.67,0.87)
Including only events before COVID-19 outbreak - RS	226/2946	316/2950	0.70 (0.59,0.83)
Including time-dependent covariate for onset of COVID-19 outbreak - RS	415/2997	511/2991	0.79 (0.69,0.90)
Treatment effect before and after COVID-19 outbreak			
Before COVID-19 outbreak - RS	226/2946	316/2950	0.70 (0.59,0.83)
After COVID-19 outbreak - RS	189/2663	195/2577	0.93 (0.76,1.13)
Including events up to 7 days prior to SARS-Cov2 infection - RS	415/2997	507/2991	0.79 (0.70,0.90)



COVID-19 onset dates are 01 Dec 2019 for China and 01 Jan 2020 for all other countries.

SARS-CoV-2 infection was defined by broad scope BIcMQ SARS-CoV-2 infection including PT 'Suspected Covid-19'.

* There is no single definition of number of patients with an event because each imputation can produce a different number of events; 88 patients in the placebo group and 84 patients in the empagliflozin groups were lost to follow-up for the primary endpoint (prematurely discontinued trial) and had imputed data [CTR 1245.110, c31803238, Tables 10.1: 2 and 15.2.1.2: 3].

Source data: [CTR 1245.110, c31803238, Section 11.1]

In the sensitivity analyses the treatment effect for the primary endpoint appears larger before vs. after COVID-19 outbreak (before HR 0.70, 95%CI 0.59-0.83; after HR 0.93, 95%CI 0.76-1.13), with a similar number of subjects included before and after. The treatment difference may, at least partly, be explained by that during COVID outbreak, less patients were accepted for hospitalisation, but this is speculative.

Summary of main study(ies)

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

Table 19. Summary of Efficacy for trial 1245.110

Title: EMPEROR-preserved			
Study identifier	trial 1245.110		
Design	Phase III international, multi-centre, double-blind, parallel-group, placebo-controlled, event-driven trials		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		event driven, median follow up of 23 months of treatment 4-28 days 30 days
Hypothesis	Superiority		
Treatments groups	Empagliflozin 10mg		Empagliflozin 10mg once daily during study duration (median follow up of 23 months of treatment), n=2997 randomized
	placebo		Placebo during study duration (median follow up of 23 months of treatment), n=2991 randomized
Endpoints and definitions	Primary endpoint	CV death or HHF	Time to the first event of adjudicated CV death or adjudicated hospitalisation for heart failure
	Key Secondary endpoint	first and recurrent HHF	Occurrence of adjudicated HHF (first or recurrent)
		eGFR slope, change from baseline	eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline
	Secondary/ Exploratory endpoint	CV death	Time to adjudicated CV death
		All-cause mortality	Time to all-cause mortality
		Composite renal event	Time to the first event in the composite renal endpoint: chronic dialysis[1], renal transplant, or sustained[2] reduction in eGFR (CKD-EPI) [3]
		All-cause hospitalisation	Occurrence of all-cause hospitalisation (first and recurrent)
		Patient reported outcome	Change from baseline in KCCQ clinical summary score[4] at Week 52
Database lock	<date>		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Empagliflozin 10 mg	placebo
	Number of subject	2297	2291
	CV death or HHF, n (%)	415 (13.8)	511 (17.1)
	empagliflozin vs. placebo HR, 95% CI, p-value	0.79 0.69 to 0.90 P= 0.0003	
	first and recurrent HHF, n	407	541
	HR, 95% CI, p-value	0.73 0.61 to 0.88 P=0.0009	
	eGFR slope, change from baseline, Slope2 [/year], estimate (95% CI)	−1.253 (−1.465, −1.041)	−2.616 (−2.827, −2.405)
	Difference vs. placebo (95% CI) , p-value	1.363 1.064 to 1.662 P<0.0001	
	CV death, n (%)	219 (7.3)	244 (8.7)
	HR (95% CI)	0.91 (0.76 to 1.09)	
	All-cause mortality, n (%)	422 (14.1)	427 (14.3)
	HR (95% CI)	HR 1.00 (0.87 – 1.15)	
	Composite renal event, n (%)	108 (3.6)	112 (3.7)
	HR (95% CI)	0.95 (0.73 to 1.24)	
	First all-cause hospitalization, n (%)	1271 (42.4)	1340 (44.8)
	HR (95% CI)	0.92 (0.85 to 0.99)	
	KCCQ clinical summary score, change from baseline (95% CI)	4.73 (3.89 to 5.12)	3.26 (2.57 tot 3.80)
	mean diff. (95% CI)	1.32 (0.45 to 2.19)	

[1] Chronic dialysis was defined as dialysis with a frequency of twice per week or more for at least 90 days
[2] Sustained was determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (the first to last of the consecutive eGFR values)
[3] Reduction in eGFR (CKD-EPI)cr was defined as reduction in eGFR from baseline of ≥40%, eGFR <15 mL/min/1.73 m2 for patients with baseline eGFR ≥30 mL/min/1.73 m2, or eGFR <10 mL/min/1.73 m2 for patients with baseline eGFR <30 mL/min/1.73 m2
[4] KCCQ, Kansas City cardiomyopathy questionnaire; clinical summary score measures HF symptoms (frequency and burden) and physical limitations

Analysis performed across trials (pooled analyses and meta-analysis)

Meta-analysis of EMPEROR trials (1245.121 and 1245.110)

The two outcome trials were conducted globally in 24 countries. A total of 9718 randomised patients from the two trials were included in this meta-analysis. Vital status was known for 99.4% of the randomised patients. The median observation time (Q1, Q3) up to the end of the planned treatment period was about 21 (15, 29) months. Disposition, demographics, and baseline characteristics were balanced between the treatment groups; some differences were observed between EMPEROR-Preserved and EMPEROR-Reduced studies. The meta-analysis was carried out using individual patient data after both trials had been completed. The methods in the meta-analysis were consistent with those used at trial level.

Endpoints

The following endpoints were pre-specified for the meta-analysis:

- Primary endpoint (confirmatory): the time to the first event in the composite renal endpoint
- Key secondary endpoints (confirmatory):
  - Time to adjudicated CV death
  - Time to onset of diabetes mellitus (DM; defined as HbA1c ≥6.5% or as diagnosed by the investigator) in patients with pre-DM (defined as no history of DM and no HbA1c ≥6.5% before treatment, and a pre-treatment HbA1c value of ≥5.7% and <6.5%)
  - Time to all-cause mortality
- Other secondary endpoints (exploratory):
  - Time to the first event in the composite renal endpoint and all-cause mortality
  - Time to onset of DM in non-diabetic patients (including pre-DM and normal)
  - eGFR (CKD-EPI)cr slope of change from baseline (chronic slope)
  - eGFR annualised change from baseline (pre-treatment) to FU value (post-treatment) (true slope)

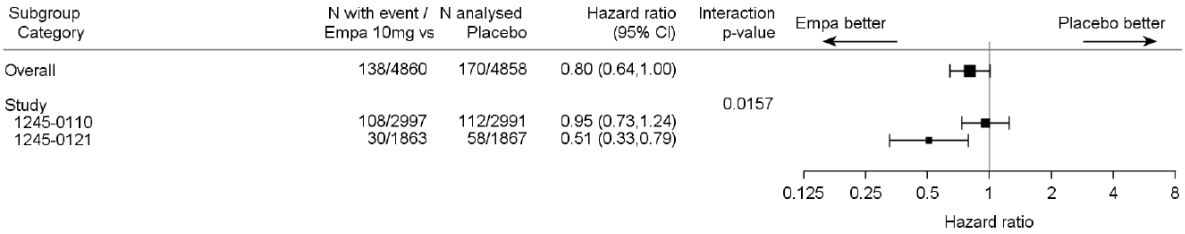
Results

Since empagliflozin was superior to placebo based on all confirmatory endpoints in the hierarchical testing in both trials, all alpha of the final analysis from the 2 trials (0.0496 from 1245.121 and 0.0497 from 1245.110) was transferred to this meta-analysis. The actual α for the meta-analysis was 0.0496 (2-sided).

In this meta-analysis, the hierarchical testing stopped after the primary endpoint (the composite renal endpoint), which did not show a statistically significant difference between empagliflozin and placebo. The 3 key secondary endpoints were therefore analysed in an exploratory manner.

For the primary endpoint, the pooled HR estimates are considered not meaningful as the 2 EMPEROR trials showed different results (treatment-by-trial interaction p = 0.0157; Figure 24). The risk was reduced with empagliflozin compared with placebo in trial 1245.121 (HFrEF) but not in 1245.110 (HFpEF; also see Figure 16), which may be attributed to differences in patient characteristics between the two studies.

Time to composite renal endpoint, overall and by trial – RS



Estimates for the trial level results in the pooled analysis could differ slightly from the results in the individual trial reports due to the combined analysis and different covariate adjustments.

Source data: [MA report, c31556490, Appendix 10, Figure 2.1.4.1.1]

For the 3 key secondary endpoints (exploratory), there was no interaction in the by-trial subgroup analyses and the pooled results showed that CV death or onset of diabetes (in patients with pre-diabetes) occurred in numerically fewer patients in the empagliflozin group than in the placebo group. The results for all-cause mortality were similar between empagliflozin and placebo.

As a secondary endpoint (exploratory), the onset of diabetes in patients without diabetes also occurred in numerically fewer patients in the empagliflozin group than in the placebo group (HR 0.85, 95% CI 0.70, 1.02), which was consistent between trials.

As another secondary endpoint (exploratory), eGFR [mL/min/1.73 m2] decline (i.e. chronic slope) was shown to be slower in the empagliflozin group than in the placebo group (difference to placebo 1.45 per year, 95% CI 1.18, 1.73), which was supported by a weighted ANCOVA analysis (difference to placebo 1.03 per year, 95% CI 0.71, 1.34) of annualised change from pre-treatment (baseline) to post-treatment (follow-up). These results were consistent between the trials.

A meta-analysis of the EMPEROR-reduced and -preserved was performed, with as primary endpoint the time to the first event in the composite renal endpoint. The hierarchical testing stopped after the primary endpoint, which did not show a statistically significant difference between empagliflozin and placebo. The Applicant describes that the pooled HR estimates are considered not meaningful as the 2 EMPEROR trials showed different results (treatment-by-trial interaction p = 0.0157). Based on the additional data provided by the Applicant, there is a smaller treatment effect of empagliflozin on the eGFR slope in EMPEROR-Preserved compare to in the EMPEROR-Reduced. Explanations for this finding are speculative but may be related to the higher SBP in patients with HFpEF, which may lead to different vessel architecture or intrarenal patho-mechanisms such as less inflammation. This could be important in view of anti-inflammatory effects being proposed for SGLT2i.

Clinical studies in special populations

A subgroup analysis based on age was performed (see above). This showed a similar or possible larger treatment effect on the primary endpoint for patients ≥70 years vs <70 years (<70 years HR 0.88, 95%CI 0.70 – 1.11; ≥70 years HR 0.75, 95%CI 0.64 – 0.87).

The applicant was requested to discuss if the recommendation in section 4.2 and 4.4 of the SmPC for the population aged ≥85 years is still suitable based on the efficacy and safety data collected for empagliflozin and if this may differ per indication. In the response, the applicant provided the efficacy data below.

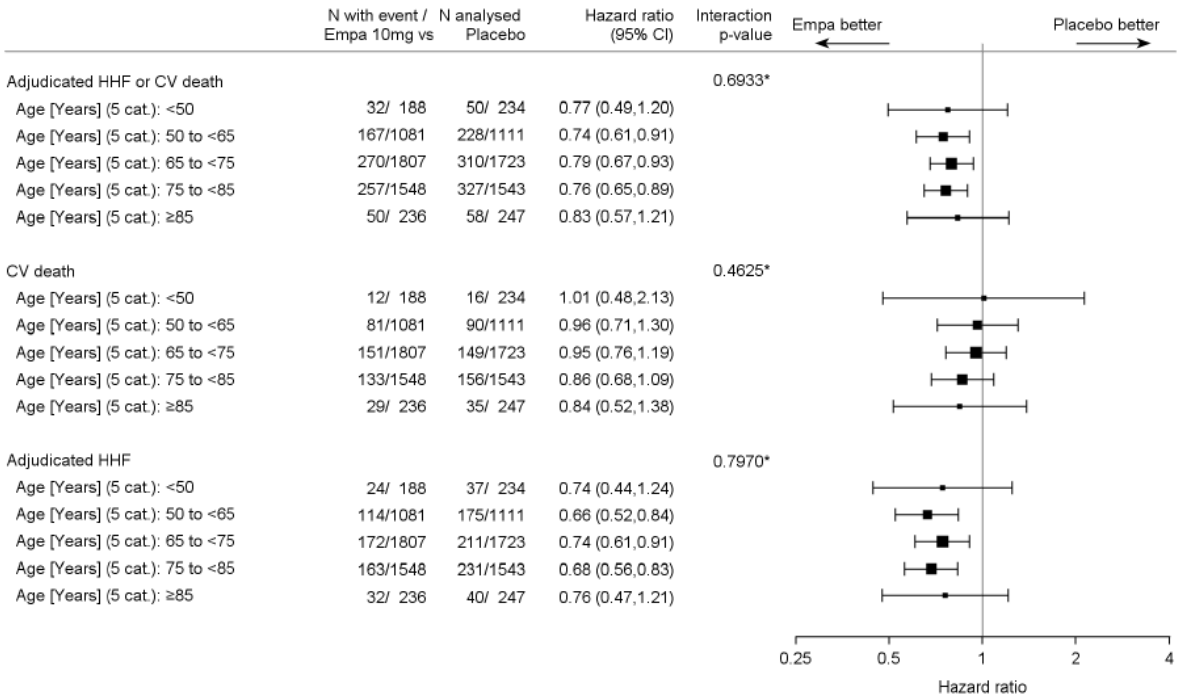
As pre-specified in the individual EMPEROR CTRs, the subgroup analyses showed consistent results for the confirmatory endpoints by age categories (< and ≥65 years in EMPEROR-Reduced; < and ≥70 years in EMPEROR-Preserved). Moreover, age analysed as a continuous variable had no relevant impact on the results of the primary endpoint (treatment-by-age interaction p = 0.2366 for EMPEROR-Reduced and 0.5162 for EMPEROR-Preserved).

In the two EMPEROR trials, a meaningful number of patients aged ≥85 years were included (a total of 483 patients), with fewer patients from EMPEROR-Reduced (58 patients in the empagliflozin group and 41 patients in the placebo group) than EMPEROR-Preserved (178 and 206 patients) [CTR 1245.121, c28576542, Table 15.1.4: 1; CTR 1245.110, c31803238, Table 15.1.4: 1].

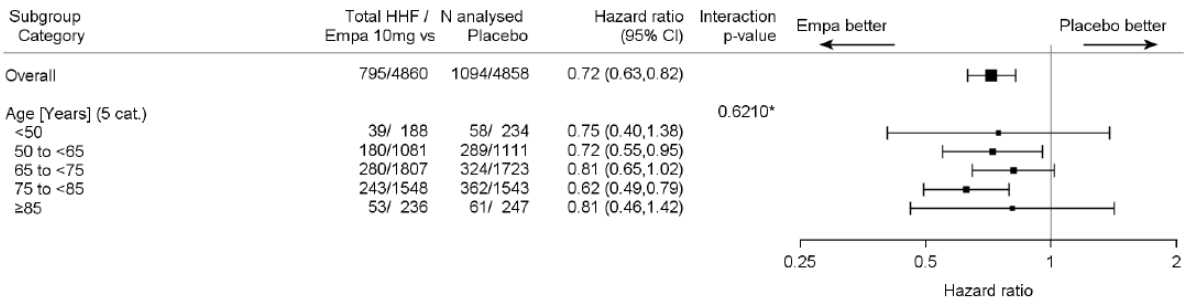
In order to increase the sample size for more precise estimations in smaller subgroups, the two trials were pooled for the analyses by age using 5 categories. The results showed that the beneficial effects of empagliflozin treatment compared with placebo were independent of age (see Figure 25).

Figure 25. Efficacy endpoints by age categories in pooled EMPEROR trials (*post hoc*)

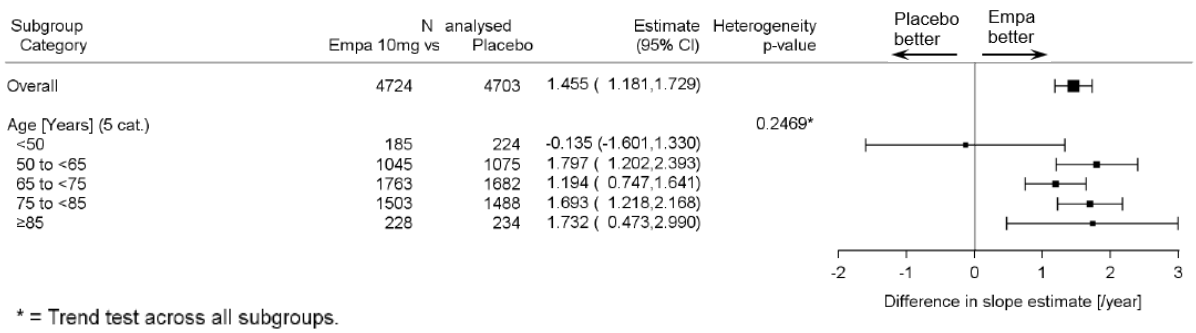
Primary endpoint: time to the first CV death or HHF and components, Cox regression, RS



Key secondary endpoint: HHF (first and recurrent), joint frailty model, RS



Key secondary endpoint: eGFR [mL/min/1.73 m2] slope, random intercept random slope model, TS (on-treatment)



* = Trend test across all subgroups.

For renal function subgroup analyses have also been performed, described above, showing a similar result across eGFR subgroups.

Supportive study(ies)

EMPA-VISION (trial 1245.1480)

Trial 1245.148 (EMPA-VISION) was a randomised, placebo-controlled, double-blind, parallel-group, 12-week trial to assess the effect of empagliflozin on cardiac physiology and metabolism. A total of 72 patients were randomised, with 36 each in the HFrEF cohort (LVEF ≤40%) or the HFpEF cohort (LVEF ≥50%), in a 1:1 ratio to empagliflozin 10 mg or placebo within the cohort. The primary endpoint was the change from baseline to Week 12 in phosphocreatine to adenosine triphosphate (PCr/ATP) ratio in the resting state measured by 31P cardiac magnetic resonance spectroscopy. The primary analysis was based on the per-protocol set of patients with PCr/ATP measurements at baseline and Week 12, and using an ANOVA model.

In the HFrEF cohort, 17 patients in the empagliflozin group and 18 in the placebo group were assessed for the primary endpoint. There was no significant difference between empagliflozin and placebo, with an adjusted mean change of -0.179 (SE 0.117) for empagliflozin vs 0.068 (SE 0.114) for placebo. The adjusted mean treatment difference was -0.247 (95% CI: -0.582, 0.087; p = 0.1418).

In the HFpEF cohort, 13 patients in the empagliflozin group and 11 in the placebo group were assessed for the primary endpoint. The most common reason for missing data at Week 12, and consequent exclusion from the primary analysis, was that due to COVID-19 pandemic restrictions, patients were unable to attend face-to-face visits from 24 Mar 2020 onwards. There was no significant difference between empagliflozin and placebo, with an adjusted mean change of 0.100 (SE 0.143) for empagliflozin vs 0.259 (SE 0.156) for placebo. The adjusted mean treatment difference was -0.159 (95% CI: -0.604, 0.286; p = 0.4650).

Imbalances in important baseline characteristics, a study population with fewer than expected patients with a history of diabetes, along with fewer patients than planned contributing to the HFpEF analysis (due to COVID-19 restrictions), may have limited the efficacy findings of interest in this trial.

EMPERIAL-preserved (1245.167)

The EMPERIAL-preserved trial (1245.167) was described in a previous application for the indication chronic heart failure with reduced ejection fraction. Trial 1245.167 was a randomised, placebo-controlled, double-blind, parallel-group, 12-week trial to assess the effect of empagliflozin on functional capacity. The eligibility criteria in the EMPERIAL-preserved trial were generally similar to those in the EMPEROR-preserved trial. The additional EMPERIAL trial was comparable regarding the screening and treatment, except for the treatment duration. The EMPERIAL trials were not event-driven but were designed to investigate the short-term (12 weeks) effect of empagliflozin on functional capacity, signs and symptoms of heart failure, and quality of life. Therefore, a treatment duration of 12 weeks was implemented. The EMPERIAL-preserved trial included 315 subjects.

The following endpoints were pre-specified:

Primary endpoint:

- change from baseline to Week 12 in the 6-minute-walk test (6MWT) distance

Key secondary endpoints:

- Change from baseline to Week 12 in KCCQ-TSS (, total symptom score)
- Change from baseline to Week 12 in CHQ-SAS (chronic heart failure questionnaire self-administered standardised format) dyspnoea score

In 1245.167, of the 315 randomised patients treated with study medication, 301 (95.6%) completed the trial, and 291 (92.4%) completed the treatment with study medication. There were no relevant differences between the treatment groups.

The primary endpoint (change from baseline to Week 12 in the 6MWT distance) did not show a statistically significant difference between empagliflozin and placebo. The two key secondary endpoints (change from baseline to Week 12 in KCCQ-TSS and in CHQ-SAS dyspnoea score) were therefore tested in an exploratory fashion. No meaningful differences between treatment groups were observed in the efficacy endpoints in 1245.167 (HFpEF).

The EMPERIAL-preserved trial was designed to evaluate the effect of empagliflozin 10 mg versus placebo on functional capacity and HF-related symptoms. The results of these studies address whether symptomatology improves after short-term treatment. The primary endpoint (change from baseline to Week 12 in the 6MWT distance) did not show a statistically significant difference between empagliflozin and placebo. This, therefore, does not support a beneficial effect of empagliflozin on functional capacity. The EMPA-VISION was a trial to assess the effect of empagliflozin on cardiac physiology and metabolism and included a small number of subjects (empagliflozin n=17, placebo n=18). In this trial also, there was no significant difference between empagliflozin and placebo. The Applicant describes that imbalances in important baseline characteristics and the small number of subjects may have hampered the efficacy results.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant states that the trial was performed in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH GCP.

No dose finding study has been performed. This is considered acceptable based on the data for the indication of T2DM and HFrEF, but it cannot be excluded that a lower dose than 10 mg is effective for the current indication.

The EMPEROR-preserved trial (1245.110) is a pivotal outcome trial and is an international, multi-centre, placebo-controlled, randomised (empagliflozin 10 mg to placebo 1:1), double-blind, and parallel-group by design in patients with HFpEF with or without T2DM. The aim of the trial is to demonstrate superiority of empagliflozin 10 mg versus placebo (empagliflozin 10 mg to placebo 1:1) in reducing the risk of hospitalisation for HF and of cardiovascular death in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms. The trial consisted of an event-driven study duration, followed by a 30-days period off study-drug. The design of the trial is acceptable and in line with the EMA guideline "Clinical investigation of medicinal products in the treatment of chronic heart failure" (CPMP/EWP/235/95, Rev.2).

The inclusion criteria consisted of age ≥ 18 years, eGFR ≥ 20 and a LVEF >40%. Although HFpEF has been defined from a LVEF >40%, the range between 40 and 50% is currently considered HFmEF and this group of patients may differ in the aetiology and treatment response compared to patients with LVEF >50%/HFpEF. Retrospective analyses have suggested that the benefits of neurohormonal antagonists in patients with HFrEF extend to those with a mildly reduced ejection fraction (Dewan P et al. Eur J Heart Fail 2020). This may affect the interpretation of the overall efficacy results. However, stratified randomisation was performed for LVEF subgroups (i.e. LVEF <50%, LVEF 50-<60% and LVEF ≥60%).

Known causes for HFpEF are infiltrative diseases, such as amyloidosis, but this was an exclusion criteria. The Applicant has put forward several reasons for excluding these subjects from the study (diagnosis made quite late, poor prognosis or [Takotsubo cardiomyopathy] could completely resolve). It was assessed that patients known to have one of these conditions would have a substantially different risk of a primary outcome event than the rest of the study population. This implies that the B/R could be quite different from the rest of the study population and it has not been studied specifically. The Applicant included a warning in section 4.4 of the SmPC, describing that efficacy in these patients has not been established. This is acceptable.

The other described exclusion criteria are in general reasonable and do not seem to hamper the translation of the trial results to the general HFrEF population at large in clinical practice.

The primary endpoint, i.e. combined CV endpoint of adjudicated CV death or adjudicated HHF, is considered adequate for the current application and in line with the EMA guideline (CPMP/EWP/235/95, Rev.2). For the key secondary renal endpoint, the eGFR (CKD-EPI)cr slope of change from baseline was analysed. This endpoint has the limitation that a long treatment period, i.e. more than 2 years, is considered needed to confirm a beneficial effect. A combined renal endpoint (i.e. chronic dialysis, renal transplant, or sustained reduction in eGFR) would have been preferred, although it is acknowledged that an analysis based on this clinical endpoint is difficult in this population with a broad eGFR range and considering the time frame and number of patients needed to demonstrate any reasonable effect.

COVID-19 had effect on the conduct of the study as 31.8% of patients had at least one visit affected by COVID-19 and these visits were often performed by phone instead of on-site. It is not considered likely that this affected the primary endpoint or other endpoints related to HHF or CV death/all-cause mortality. The adjudication of outcome events by the CEC was performed based on uploaded source documents. The adjudicated endpoints were therefore protected from being impacted. Also, for the other endpoints, it is not considered likely that it affected the outcome, as data are considered to be missing completely at random.

Statistical methods

The statistical analyses in the trial design are based on an intention to treat analysis, and the primary analysis was a Cox regression with adjudicated CV death or HHF as the primary endpoint with non-CV death as a competing event. This is acceptable. The secondary endpoint of recurrent hospitalisations is analysed using a joint frailty model. This will adjust the analysis of recurrent hospitalisations for the competing event of CV death and is acceptable. The MAH performed additional analyses testing the influence of using CV or overall mortality in the primary and key secondary composite endpoints, and the effect of the analysis model incorporating recurrent events in the secondary endpoint.

Cumulative incidence function curves that account for competing risks (i.e. non-CV deaths) and Kaplan-Meier curves of time to censoring were displayed.

The secondary endpoint eGFR slope is analysed with a random coefficient model. Since this allows for a random intercept, testing a difference in the (random) slope will not reflect the overall treatment effect, since the initial dip will be largely incorporated in the intercept. As a sensitivity analysis, an ANCOVA was performed to analyse the overall treatment effect of the change from baseline ignoring the path taken and this is considered acceptable.

Efficacy data and additional analyses

Trial 1245.110 included a large number of subjects (n=5988). Demographics and baseline characteristics were balanced between the treatment groups. The proportion of female subjects (44.7%) is remarkably

larger compared to trials performed with HFrEF and the EMPEROR-reduced trial (i.e. 23.9% female). This is not unexpected, as HFpEF is more common than HFrEF in female patients. The average age was 71.9 years (SD 9.4) and the majority of patients was White; 75.9% White, 13.8% Asian, and 4.3% Black/African American. About half of patients (48.9%) had T2DM, 10 patients (0.2%) had T1DM. Half of the patients (49.9%) had an eGFR of <60 mL/min/1.73 m2 and half of the subjects had atrial fibrillation (51.0%). The majority of the patients were in NYHA class II (81.5%) and the cause of HF was hypertensive (36.5%) or ischaemic (35.4%). This appears in line with the target population, supporting external validity of the results.

The distribution of patients between the LVEF subgroups was also equal between the three subgroups (LVEF <50% n=1983 (33.1%), LVEF 50%-<60% n=2058 (34.4%), LVEF >60% n=1947 (32.5%)). As the group of LVEF <50% may be considered as HFmEF and not comparable to the higher LVEF subgroups, it is relevant that the higher LVEF subgroups consist of a large proportion of the overall sample size.

Median exposure to study medication was about 23 months in both treatment groups, with 84% of patients treated for at least 1 year. This is an acceptable duration to evaluate the treatment effects on efficacy and safety for this application.

CV death or HHF (primary endpoint) occurred in a lower proportion of patients in the empagliflozin group than in the placebo group (empagliflozin 415/2997, 13.8%; placebo 511/2991, 17.1%), and the risk of CV death or HHF was reduced with empagliflozin treatment compared with placebo (HR empagliflozin vs placebo 0.79; 95%CI 0.69 to 0.90, p = 0.0003). This effect appears similar to the effect of empagliflozin in patients with HFrEF in the EMPEROR-reduced trial (HR 0.75, 95%CI 0.65 - 0.86), but with higher NNT (EMPEROR-preserved NNT 31, EMPEROR-reduced NNT 19). The separation of the estimated cumulative incidence of CV death or first HHF between empagliflozin and placebo started shortly after randomisation and was maintained throughout the trial. These findings support a beneficial effect of treatment with empagliflozin. The difference in treatment effect appears mainly due to the decrease in HHF, as CV death as the first did not differ between the treatment groups (empagliflozin n=156 (5.2%), placebo n=159 (5.3%)), but the total number of CV death (described below) was lower with empagliflozin vs placebo, but the difference was not statistically significant (empagliflozin 219/2997, placebo 244/2991, HR 0.91, 95%CI 0.76 – 1.09).

All-cause mortality was similar in both treatment groups (HR 1.00, 95%CI 0.87 – 1.15). The number of non-CV death was larger with empagliflozin, but this difference was not statistically significant (empagliflozin 203/2997, placebo 183/2991, HR 1.13, 95%CI 0.92 – 1.38). The Applicant provided an evaluation of the causes of non-CV death, and this did not show a specific increase in a cause of death during empagliflozin treatment.

An initial dip in eGFR was observed with empagliflozin treatment, followed by a slower decrease in eGFR over time. This is in line with results in previous trials performed with SGLT2i. The change of eGFR slope from baseline was a key secondary endpoint and showed a slower decline in eGFR in the empagliflozin group, with an estimated difference in slope of 1.363 mL/min/1.73 m2 per year vs placebo (99.9% CI 0.861 to 1.865; p<0.0001). But the effect on slope can only be interpreted if seen in conjunction with intercept. The applicant also provided an analysis of change from baseline using ANCOVA, similar to the previous application for the HFrEF indication. This resulted in a larger or similar decrease in eGFR for empagliflozin vs. placebo (change from baseline: empagliflozin -6.4, placebo -6.0, comparison -0.4 (-1.2, 0.3)). But after the 30 day follow-up period after stop of treatment, the decrease in eGFR was smaller for the empagliflozin group (change from baseline: empagliflozin -3.3, placebo -5.7, comparison 2.4 (1.6, 3.2)), supporting that the initial dip is reversable. The effect on the renal composite endpoint is, however, considered preferred for evaluation of renal effects. In the current trial, the effect of empagliflozin on the eGFR slope is not supported or confirmed by the observed effects on the composite renal endpoint (i.e. chronic dialysis, renal transplant, or sustained reduction in eGFR), as the results are similar for empagliflozin vs. placebo

(empagliflozin 108/2997 (3.6%), placebo 112/2991 (3.7%), HR 0.95 95%CI 0.73, 1.24). However, the Applicants supports the findings with other additional pre-specified analyses, i.e. eGFR change from pre-treatment (baseline) to post-treatment (follow-up; FU) analysed with ANCOVA, "true slope" (annualised change from pre-treatment to post-treatment weighted by time of FU squared) and progression to or reversal from macro-albuminuria. Although all exploratory, these findings indicate a consistent finding and this appears clinical relevant.

A meta-analysis of the EMPEROR-reduced and -preserved was performed with as primary endpoint the time to the first event in the composite renal endpoint. The hierarchical testing stopped after the primary endpoint, which did not show a statistically significant difference between empagliflozin and placebo. The Applicant describes that the pooled HR estimates are considered not meaningful as the 2 EMPEROR trials showed different results (treatment-by-trial interaction p = 0.0157). This composite of major adverse renal outcomes was significantly lower in the EMPEROR-Preserved trial than in the EMPEROR-Reduced trial. Based on the additional data provided by the Applicant, there is a smaller treatment effect of empagliflozin on the eGFR slope in EMPEROR-Preserved than in EMPEROR-Reduced. Explanations for this finding are speculative but may be related to the higher SBP in patients with HFpEF.

The effects of empagliflozin were accompanied by effects on body weight, improvement in NYHA classification and reduction in systolic blood pressure. This is in line with previous observations with SGLT2i treatment.

The change from baseline in KCCQ clinical summary score at Week 52 was a secondary/exploratory endpoint. The mean treatment difference in change was 1.32, 95% CI 0.45 to 2.19. Although statistically significant, the treatment difference appears modest, and the clinical relevance is questionable. The Applicant also provided the proportion of patients achieving a clinically relevant change (i.e. 5 points). This endpoint resulted in a larger proportion of patients with clinically relevant change (empagliflozin 1126 patients, 41.7%; placebo 1034 patients, 38.7%), but the difference in percentage is small. For other KCCQ scores, a treatment difference was also observed, supporting a consistent finding, but the treatment differences are again considered small and not clinically relevant.

Subgroup analyses were performed for the primary and key secondary endpoints. Important is the subgroup analyses for LVEF. Although p for interaction was not significant (p=0.2098) for the primary endpoint (CV death or HHF), the effect was more pronounced in patients with LVEF <50% compared to ≥60%, but was positive for all LVEF subgroups and still significant for the group LVEF 50-<60% (LVEF <50% empagliflozin 145/995, placebo 193/988, HR 0.71, 95%CI 0.57-0.88; LVEF 50-<60% empagliflozin 138/1028, placebo 173/1030, HR 0.80, 95%CI 0.64-0.99; LVEF >60% empagliflozin 132/974, placebo 145/973, HR 0.87, 95%CI 0.69-1.10). As the effect of empagliflozin on the primary endpoint was beneficial for all LVEF subgroups, the indication for the treatment of heart failure in patients with HFpEF is acceptable. As the indication for the treatment of heart failure is for all types of heart failure, the wording "*for the treatment of symptomatic chronic heart failure."* is considered acceptable.

It could, however, be suggested that there is a modification of the treatment effect in subjects with higher LVEF for the key secondary endpoint, i.e. adjudicated HHF (first and recurrent), where the point estimate for the subgroup LVEF ≥60% is HR 1.06 (95%CI 0.76-1.46) and p for interaction 0.0077. This could indicate that patients with LVEF ≥60% benefit less from treatment with empagliflozin. The Applicant performed additional post-hoc analyses with subgroups by LVEF in more detail for the HF outcomes, using a 5% increment of LVEF to categorise patients for this secondary endpoint and for the primary endpoint. For first HHF in the subgroup LVEF 60 to <65% the hazard ratio was 0.75 (95%CI 0.51 – 1.10). The HR was >1 in subgroup LVEF 65 to <70% (HR 1.57, 95%CI 0.92 – 2.70), but in subgroup LVEF ≥70% the HR was again <1 (HR 0.55, 95%CI 0.29 to 1.06). Notably, the number of subjects is low in this latter subgroup (subjects n=319), but the lower HR in the subgroup ≥70%, contradicts the suggestions of a decrease in effect in higher LVEF subgroup. For the analyses of total occurrence of HHF (first and

recurrent), the HR was >1 for two subgroups, i.e. subgroup LVEF 60 to <65% (HR 1.04, 95%CI 0.66 – 1.65) and LVEF 65 to <70% (HR 1.86, 95%CI 1.03 – 3.35). But again, the subgroup LVEF ≥70% had a HR <1 (HR 0.42, 95%CI 0.20 - 0.88). The recurrent HHF appears to mainly contribute to the finding of a higher hazard ratio for the subgroup LVEF ≥60% in the secondary endpoint. The analyses on the contribution of HHF events by number of events experienced per patient showed that for patients who had 4 or more events, in the subgroup of LVEF of 65 to <70% 6 patients in the empagliflozin arm had 31 events while 1 patient in the placebo arm had 5 events. This may contribute to the imbalance in the analysis of the recurrent HHF in this subgroup. This may be related to chance. Based on these findings it is not considered supported that there is a decrease in efficacy in patients with higher LVEF.

Although effectiveness of treatment with ACEi/ARB, MRA's and/or ARNI's have not been demonstrated in patients with HFpEF, the majority of the patients used these treatments during the trial, i.e. ACEi/ARB's, 82.6%, MRA's 46.0%, ARNI's 4.4%. Empagliflozin was, therefore, evaluated on top of these medication, but these medications are not registered for the treatment of HFpEF. The Applicant described the baseline use of these agents in the trial population in Section 5.1 of the SmPC. The subgroup analysis for baseline use of ACEi/ARB/ARNI's and/or MRA's resulted in a similar risk reduction with empagliflozin vs. placebo for the primary and key secondary endpoints for patients using these agents compared to patients not using these agents at baseline. As the efficacy of empagliflozin appears consistent with vs without the use of these agents, it is acceptable that the indication for the treatment of HFpEF is independent of the baseline use of these agents.

In elderly patients, i.e. age ≥ 70 years, the point estimate of treatment effect was larger compared to patients < 70 for the primary endpoint (age ≥70 years HR 0.75, 95%CI 0.64-0.95, age <70 years HR 0.88, 95%CI 0.70-1.11) and key secondary endpoint (HHF) (age ≥70 years HR 0.65, 95%CI 0.52-0.82, age <70 years HR 0.92, 95%CI 0.67-1.26). This supports a beneficial effect in elderly patients.

In the sensitivity analyses the treatment effect for the primary endpoint appears larger before vs. after COVID-19 outbreak (before HR 0.70, 95%CI 0.59-0.83; after HR 0.93, 95%CI 0.76-1.13), with a similar number of subjects included before and after. The treatment difference may, at least partly, be explained by that during COVID outbreak, less patients were accepted for hospitalisation, but this is speculative.

The EMPERIAL-preserved trial (n=315) was designed to evaluate the effect of empagliflozin 10 mg versus placebo on functional capacity and HF-related symptoms. The results of these small sized studies address whether symptomatology improves after short-term treatment. The primary endpoint (change from baseline to Week 12 in the 6MWT distance) did not show a statistically significant difference between empagliflozin and placebo. This, therefore, does not support a beneficial effect of empagliflozin on functional capacity.

2.4.4. Conclusions on the clinical efficacy

The results of the well-designed pivotal outcome trial 1245.110 showed a risk reduction with empagliflozin vs. placebo in patients with HFpEF for the combined cardiovascular endpoint (HHF or CV death). For the primary endpoint, this was observed across the LVEF subgroups. The wording of indication is considered acceptable. The Applicant included a warning in section 4.4 of the SmPC, describing that efficacy in patients with infiltrative diseases has not been established. This is acceptable.

2.5. Clinical safety

Introduction

Currently, empagliflozin is registered for the treatment of T2DM and for chronic heart failure with reduced ejection fraction. Based on the placebo-controlled trials and post-marketing experience, known side-effects of treatment with empagliflozin are o.a. genital infections, keto-acidosis, hypoglycaemia, volume depletion and urinary tract infections. See also the table below from Section 4.8 of the current SmPC of Jardiance (Table 20).

Table 20. Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience

System organ class	Very common	Common	Uncommon	Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection Urinary tract infection (including pyelonephritis and urosepsis)		Necrotising fasciitis of the perineum (Fournier´s gangrene)[a]
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)	Thirst		Diabetic ketoacidosis
Gastrointestinal disorders		Constipation		
Skin and subcutaneous tissue disorders		Pruritus (generalised) Rash	Urticaria Angioedema	
Vascular disorders	Volume depletion			
Renal and urinary disorders		Increased urination	Dysuria	
Investigations		Serum lipids increased	Blood creatinine increased/ Glomerular filtration rate decreased Haematocrit increased	

a In the EMPEROR-Reduced heart failure study, one case (<0.1%) of necrotising fasciitis of the perineum (Fournier´s gangrene) was observed in a patient with heart failure and diabetes mellitus treated with empagliflozin.

The main objective of the below described safety evaluation is to present and evaluate safety data on the clinical use of empagliflozin in patients with chronic heart failure. The trials included patients with and without T2DM.

The described safety analyses followed the "treatment-emergent" principle and included all treated patients (TS). Unless otherwise specified, treatment was assigned as randomised and the analyses of AEs were based on the number of patients with AEs. AE analyses were restricted to "on-treatment" AEs, defined as

AEs with an onset date between the first trial medication intake and 7 days after the last intake, unless otherwise stated. Exposure-adjusted AEs were also displayed as incidence rates per 100 patient-years.

In addition to the safety analyses of trials 1245.110 (EMPEROR-Preserved) and 1245.148 (EMPA-VISION) presented in CTRs, safety data of 5 trials in patients with chronic HF were pooled as "SAF-HF1", regardless of LVEF category.

Patient exposure

In SAF-HF1, 10408 patients were treated. The majority of the patients were from the two EMPEROR trials (Table 21).

Table 21. Number of treated patients in SAF-HF1

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
SAF-HF1 – TS	5202 (100.0)	5206 (100.0)	10408 (100.0)
1245.110 (EMPEROR-Preserved)	2989 (57.5)	2996 (57.5)	5985 (57.5)
1245.121 (EMPEROR-Reduced)	1863 (35.8)	1863 (35.8)	3726 (35.8)
1245.148 (EMPA-VISION)	36 (0.7)	35 (0.7)	71 (0.7)
1245.167 (EMPERIAL-preserved)	158 (3.0)	157 (3.0)	315 (3.0)
1245.168 (EMPERIAL-reduced)	156 (3.0)	155 (3.0)	311 (3.0)
North America	703 (13.5)	695 (13.3)	1398 (13.4)
Latin America	1402 (27.0)	1399 (26.9)	2801 (26.9)
Europe	2233 (42.9)	2242 (43.1)	4475 (43.0)
Asia	587 (11.3)	591 (11.4)	1178 (11.3)
Other[1]	277 (5.3)	279 (5.4)	556 (5.3)

1 Included the countries Australia, India, and South Africa

Source data: [SCS appendix 2, c35146126, Tables 1.1.1 and 1.1.2]

Of the 10408 treated patients in SAF-HF1, 7472 patients (71.8%) completed treatment as planned, and 2936 patients prematurely discontinued study medication (28.2%, including patients who died). The most common reason for premature discontinuation of study medication was AE (17.7%, including fatal events; Table 22).

Table 22. Disposition of treated patients in SAF-HF1

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Screened			20309
Randomised			10417
Treated	5202 (100.0)	5206 (100.0)	10408 (100.0)
Completed treatment	3722 (71.5)	3750 (72.0)	7472 (71.8)
Prematurely discontinued study medication	1480 (28.5)	1456 (28.0)	2936 (28.2)
Adverse event	916 (17.6)	931 (17.9)	1847 (17.7)
Non-compliance with protocol	36 (0.7)	29 (0.6)	65 (0.6)
Lost to follow-up	17 (0.3)	34 (0.7)	51 (0.5)
Withdrawal by patient	432 (8.3)	378 (7.3)	810 (7.8)
Other reason	73 (1.4)	83 (1.6)	156 (1.5)
Reason missing	6 (0.1)	1 (<0.1)	7 (0.1)

Patients are presented as randomised except for trial 1245.148 (as treated).

Source data: [SCS appendix 2, c35146126, Table 1.1.3]

In SAF-HF1, the median exposure to study medication was about 18 months in both treatment groups, with 70.2% of patients treated for at least 1 year (Table 23.).

Table 23. Exposure to study medication in SAF-HF1 – TS

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	5202 (100.0)	5206 (100.0)	10408 (100.0)
Exposure categories, N (%)			
≥12 weeks	4825 (92.8)	4865 (93.4)	9690 (93.1)
≥26 weeks	4321 (83.1)	4370 (83.9)	8691 (83.5)
≥52 weeks	3644 (70.0)	3659 (70.3)	7303 (70.2)
≥78 weeks	2542 (48.9)	2520 (48.4)	5062 (48.6)
≥104 weeks	1603 (30.8)	1589 (30.5)	3192 (30.7)
≥156 weeks	308 (5.9)	303 (5.8)	611 (5.9)
Duration of exposure [months]			
Median (Q1, Q3)	17.87 (9.63, 26.63)	17.83 (9.87, 26.67)	17.83 (9.78, 26.63)
Mean (SD)	18.42 (10.95)	18.50 (10.86)	18.46 (10.90)
Total exposure [years]	7871.7	7912.4	15784.1

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

Source data: [SCS appendix 2, c35146126, Table 1.3.1]

Adverse events

In SAF-HF1, the frequencies of patients with at least one AE, severe AEs, and AEs leading to treatment discontinuation were similar between empagliflozin and placebo. The frequency of investigator-defined drug-related AEs was higher in the empagliflozin group than in the placebo group. The frequency of patients with SAEs was lower in the empagliflozin group than in the placebo group (Table 24.). The most frequent events in these categories are described below.

Table 24. Overall summary of adverse events in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Empa 10 mg N (%)
Number of patients	5202 (100.0)	5206 (100.0)
Patients with any AEs	4234 (81.4)	4164 (80.0)
Severe AEs	1378 (26.5)	1265 (24.3)
Investigator defined drug-related AEs	669 (12.9)	810 (15.6)
AEs leading to discontinuation of study medication	899 (17.3)	912 (17.5)
Serious AEs	2502 (48.1)	2250 (43.2)
Results in death	481 (9.2)	472 (9.1)
Is life threatening	206 (4.0)	199 (3.8)
Persistent or significant disability/incapacity	61 (1.2)	78 (1.5)
Requires or prolongs hospitalisation	1912 (36.8)	1735 (33.3)
Other medically important serious event	1129 (21.7)	970 (18.6)

Percentages calculated using total number of patients per treatment as the denominator.

A patient may be counted in more than 1 seriousness criterion.

Source data: [SCS, c35218777, Section 2.1.1]

Most frequently reported AEs

Adverse events were most frequently reported in the SOCs cardiac disorders (empagliflozin 1548 patients, 29.7% vs placebo 1822 patients, 35.0%), infections and infestations (1700 patients, 32.7% vs 1732 patients, 33.3%), and metabolism and nutrition disorders (1241 patients, 23.8% vs 1446 patients, 27.8%) (Table 25). On the PT level, the most frequently reported AE were cardiac failure (795 patients, 15.3% vs 1065 patients, 20.5%), hypotension (372 patients, 7.1% vs 313 patients, 6.0%), and renal impairment (320 patients, 6.1% vs 312 patients, 6.0%). Preferred terms with a higher frequency in the empagliflozin group than in the placebo group were urinary tract infection and hypotension. Adverse events with PTs reported in ≥5.0% of patients in at least one group are summarised in the table below

Table 25. Patients with adverse events in SAF-HF1 (frequency ≥5.0% in at least one treatment group at the PT level) – TS

MedDRA SOC MedDRA PT	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Total with adverse events	4234 (81.4)	157.84	4164 (80.0)	142.94
Cardiac disorders	1822 (35.0)	29.17	1548 (29.7)	23.39
Cardiac failure	1065 (20.5)	15.20	795 (15.3)	10.78
Atrial fibrillation	318 (6.1)	4.14	283 (5.4)	3.66
Infections and infestations	1732 (33.3)	28.31	1700 (32.7)	27.23
Urinary tract infection	259 (5.0)	3.35	314 (6.0)	4.07
Pneumonia	291 (5.6)	3.77	257 (4.9)	3.29
Metabolism and nutrition disorders	1446 (27.8)	22.93	1241 (23.8)	18.76
Hyperkalaemia	330 (6.3)	4.33	282 (5.4)	3.66
Hyperuricaemia	329 (6.3)	4.35	197 (3.8)	2.54
Diabetes mellitus	263 (5.1)	3.43	191 (3.7)	2.45
Renal and urinary disorders	904 (17.4)	12.64	907 (17.4)	12.66
Renal impairment	312 (6.0)	4.05	320 (6.1)	4.15
Vascular disorders	899 (17.3)	12.74	847 (16.3)	11.89
Hypotension	313 (6.0)	4.09	372 (7.1)	4.87
Hypertension	299 (5.7)	3.92	264 (5.1)	3.43
Injury, poisoning and procedural complications	568 (10.9)	7.73	609 (11.7)	8.23
Fall	249 (4.8)	3.24	261 (5.0)	3.37

Source data: [SCS appendix 2, c35146126, Table 2.1.1.3]

The number of AEs and severe AEs were similar for empagliflozin compared to placebo, but the number of cardiac events is lower for empagliflozin vs. placebo, and the similar number of total AEs could therefore result in a larger number of other AEs. Based on the most frequently reported AEs, this number of events is also similar for empagliflozin compared to placebo, except for hypotension (empagliflozin 372 (7.1%) placebo 313 (6.0%)) and urinary tract infections (empagliflozin 314 (6.0%) placebo 259 (5.0%)). Hypotension is a known side-effect for SGLT2i treatment and can be related to other symptoms, such as syncope and fall, discussed below. Urinary tract infections are also known side effects of SGLT2i treatment.

AEs by worst intensity

Adverse events were primarily of mild or moderate intensity (Table 26). The frequencies of patients with severe AEs were similar between treatment groups. On the PT level, proportions of patients with AEs of

severe intensity with a frequency ≥1.0% in at least one treatment group were also similar between groups and are summarised in the table below

Table 26. Patients with AEs by worst intensity and the most frequent severe AEs (frequency >1.0% in at least one treatment group at the PT level) in SAF-HF1 – TS

	Placebo N (%)	Empa 10 mg N (%)
Number of patients	5202 (100.0)	5206 (100.0)
Patients with any AEs		
Mild	1167 (22.4)	1243 (23.9)
Moderate	1689 (32.5)	1656 (31.8)
Severe	1378 (26.5)	1265 (24.3)
Patients with severe AEs		
MedDRA SOC		
MedDRA PT		
Cardiac disorders	692 (13.3)	561 (10.8)
Cardiac failure	398 (7.7)	293 (5.6)
Infections and infestations	248 (4.8)	271 (5.2)
Pneumonia	90 (1.7)	76 (1.5)
General disorders and administration site	138 (2.7)	144 (2.8)
Death[1]	65 (1.2)	76 (1.5)
Renal and urinary disorders	147 (2.8)	121 (2.3)
Acute kidney injury	69 (1.3)	49 (0.9)

1 Deaths not attributed to another PT by the investigator. The frequencies of patients with fatal AEs were balanced between treatment. Source data: [SCS appendix 2, c35146126, Table 2.1.1.4]

The number of AEs with worst intensity were not more frequent during empagliflozin treatment compared to placebo.

Adverse events of special interest (AESIs) and specific AEs

The safety analyses were also focused on AESIs and specific AEs that represent specific medical concepts of interest with all relevant PTs analysed together.

In SAF-HF1, the overall frequencies of patients with acute renal failure, ketoacidosis, AEs leading to LLA, confirmed hypoglycaemic events, bone fractures, and urinary tract malignancies were similar in the empagliflozin group and in the placebo group (Table 27). Urinary tract infections, genital infections, and volume depletion, including hypotension, were more common in the empagliflozin group than in the placebo group. Fewer patients in the empagliflozin group had hepatic injury events. The frequencies of patients with AEs leading to treatment discontinuation were below 1% in any category of AESIs or specific AEs except for acute renal failure (which was balanced between groups).

Table 27. Overall summary of AESIs and specific AEs in SAF-HF1 – TS

Category of AESIs and specific AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Acute renal failure (narrow SMQ)	587 (11.3)	7.82	547 (10.5)	7.27
Serious	262 (5.0)	3.36	184 (3.5)	2.33

Leading to discontinuation	61 (1.2)	0.77	54 (1.0)	0.68
Hepatic injury (narrow SMQs)	248 (4.8)	3.20	197 (3.8)	2.51
Serious	60 (1.2)	0.76	46 (0.9)	0.58
Leading to discontinuation	12 (0.2)	0.15	10 (0.2)	0.12
Up to 30 days after treatment discontinuation	256 (4.9)	3.20	205 (3.9)	2.53
Ketoacidosis (broad BIcMQ)	77 (1.5)	0.97	63 (1.2)	0.79
Ketoacidosis (narrow BIcMQ)	6 (0.1)	0.08	4 (0.1)	0.05
AEs leading to LLA up to trial completion (investigator-defined)[1, 2]	33/4852 (0.7)	0.37	29/4859 (0.6)	0.32
Urinary tract infection (BIcMQ)	335 (6.4)	4.37	402 (7.7)	5.27
Complicated	62 (1.2)	0.78	78 (1.5)	0.98
Leading to discontinuation	21 (0.4)	0.26	34 (0.7)	0.42
Genital infection (BIcMQ)	35 (0.7)	0.44	101 (1.9)	1.28
Complicated	14 (0.3)	0.18	14 (0.3)	0.18
Leading to discontinuation	2 (<0.1)	0.03	15 (0.3)	0.19
Volume depletion (narrow BIcMQ)	483 (9.3)	6.44	566 (10.9)	7.59
Hypotension (BIcMQ, subset of vol. depl.)	430 (8.3)	5.69	499 (9.6)	6.64
Serious	77 (1.5)	0.97	101 (1.9)	1.27
Leading to discontinuation	15 (0.3)	0.19	25 (0.5)	0.31
Symptomatic hypotension (investigator-defined)[2, 3]	262/5166 (5.1)	3.40	309/5171 (6.0)	4.02
Confirmed hypoglycaemic events[4]	108 (2.1)	1.38	101 (1.9)	1.28
In patients with T1DM[2]	1/5 (20.0)	18.81	2/5 (40.0)	24.29
In patients with T2DM[2]	89/2574 (3.5)	2.33	82/2565 (3.2)	2.15
In patients with pre-diabetes[2]	12/1708 (0.7)	0.46	10/1729 (0.6)	0.38
In patients without diabetes or pre-diabetes[2]	6/912 (0.7)	0.43	7/904 (0.8)	0.50
Bone fracture (BIcMQ)	171 (3.3)	2.20	182 (3.5)	2.32
Serious	82 (1.6)	1.04	91 (1.7)	1.15
Leading to discontinuation	3 (0.1)	0.04	6 (0.1)	0.07
Up to trial completion	196 (3.8)	2.20	212 (4.1)	2.38
Urinary tract malignancy up to trial completion (BIcMQ)	22 (0.4)	0.24	28 (0.5)	0.31
Patients with ≥6 months of exposure only[2]	14/4302 (0.3)	0.23	18/4343 (0.4)	0.29

SMQ, standardised MedDRA query; BIcMQ, Boehringer Ingelheim customised MedDRA query

1 Data collected only in 1245.110 and 1245.121

2 Patients with events/patients in subgroup (%)

3 Data collected only in 1245.110, 1245.121, 1245.167, 1245.168

4 Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or where assistance was required

Source data: [SCS appendix 2, c35146126, Tables 2.1.1.10, 2.2.1.5, 2.2.1.6, 2.2.2.4, 2.2.2.5, 2.2.2.6, 2.2.4.3, 2.2.5.5, 2.2.5.6, 2.2.7.5, 2.2.7.6, 2.2.9.1, 2.2.9.7, 2.2.9.8, 2.2.10.14, 2.2.11.5, 2.2.11.6, 2.2.11.7, 2.2.12.2, 2.2.12.3]

Decreased renal function

The frequencies of patients with acute renal failure (narrow SMQ) were similar in the empagliflozin group and in the placebo group; see Table 28. The most frequently reported PT within the SMQ was renal impairment. Of note, the PT acute kidney injury was reported for a lower proportion of patients in the empagliflozin group than in the placebo group.

The frequency of patients with SAEs of acute renal failure was also lower in the empagliflozin group than in the placebo group. Adverse events leading to discontinuation of study medication were reported with similar frequencies in the empagliflozin group and in the placebo group.

Table 28. Patients with acute renal failure (SMQ) in SAF-HF1 – TS

MedDRA PT	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Acute renal failure (narrow SMQ)	587 (11.3)	7.82	547 (10.5)	7.27
Renal impairment	312 (6.0)	4.05	320 (6.1)	4.15
Acute kidney injury	166 (3.2)	2.11	118 (2.3)	1.49
Renal failure	141 (2.7)	1.80	131 (2.5)	1.66
Azotaemia	4 (0.1)	0.05	0	0
Nephropathy toxic	3 (0.1)	0.04	0	0
Oliguria	3 (0.1)	0.04	2 (<0.1)	0.02
Anuria	1 (<0.1)	0.01	0	0
Prerenal failure	1 (<0.1)	0.01	1 (<0.1)	0.01
Serious	262 (5.0)	3.36	184 (3.5)	2.33
Leading to discont. of study medication	61 (1.2)	0.77	54 (1.0)	0.68

Source data: [SCS appendix 2, c35146126, Tables 2.2.1.4 to 6]

Subgroup analyses were performed by age, sex, race, and baseline eGFR, diabetes status, and use of certain medications (i.e. ACE-inhibitors/ARB/ARNi, diuretics, loop/high-ceiling diuretics).

Investigator-defined decreased renal function (reported as AESI) was reported for 2.7% of patients (133 of 4894) in the empagliflozin group and 4.0% of patients (197 of 4888) in the placebo group.

In the analysis of safety laboratory parameters, the frequencies of patients with serum creatinine ≥2x the baseline value and above the normal range were 1.7% in the empagliflozin group and 2.1% in the placebo group.

Hepatic injury

The frequency of patients with hepatic injury (narrow SMQs) was lower in the empagliflozin group than in the placebo group (Table 29). The most frequent PTs were liver injury, hepatic function abnormal, and hepatic steatosis. All other PTs were reported for ≤0.2% of patients in either treatment group.

Similar frequencies between groups or lower frequencies in the empagliflozin group than in the placebo group were observed for serious hepatic injury, for events leading to discontinuation of study medication, and for all hepatic injury events when considering a longer period of up to 30 days after treatment discontinuation. Patients with diabetes and patients without diabetes showed the same trend as the overall population.

Table 29. Patients with hepatic injury (SMQ; frequency ≥0.2% in at least one treatment group at the PT level) in SAF-HF1 – TS

MedDRA PT	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	

Hepatic injury (narrow SMQs)	248 (4.8)	3.20	197 (3.8)	2.51
Liver injury	28 (0.5)	0.35	19 (0.4)	0.24
Hepatic function abnormal	26 (0.5)	0.33	24 (0.5)	0.30
Hepatic steatosis	24 (0.5)	0.30	17 (0.3)	0.21
Liver disorder	11 (0.2)	0.14	7 (0.1)	0.09
Hepatomegaly	9 (0.2)	0.11	6 (0.1)	0.07
Hepatic cirrhosis	7 (0.1)	0.09	8 (0.2)	0.10
Hyperbilirubinaemia	6 (0.1)	0.08	9 (0.2)	0.11
Congestive hepatopathy	4 (0.1)	0.05	9 (0.2)	0.11
Hepatic injury (narrow SMQs), serious	60 (1.2)	0.76	46 (0.9)	0.58
Hepatic injury (narrow SMQs) leading to discont. of study medication	12 (0.2)	0.15	10 (0.2)	0.12
Hepatic injury (narrow SMQs) up to 30 days after treatment discontinuation	256 (4.9)	3.20	205 (3.9)	2.53
With diabetes	137/2579 (5.3)	3.61	113/2570 (4.4)	2.95
Without diabetes	111/2620 (4.2)	2.81	84/2633 (3.2)	2.10

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

Source data: [SCS appendix 2, c35146126, Tables 2.2.2.3 to 7]

The frequencies of patients with elevated liver enzyme values were balanced between treatment groups (Table 30.).

Table 30. Patients with elevated liver enzyme values, up to 30 days after treatment discontinuation in SAF-HF1 – TS

Elevated liver enzymes criteria	Placebo N (%)	Empa 10 mg N (%)
Number of patients	5202 (100.0)	5206 (100.0)
ALT and/or AST ≥3x ULN	89 (1.7)	74 (1.4)
≥5x ULN	34 (0.7)	30 (0.6)
≥10x ULN	13 (0.2)	5 (0.1)
≥20x ULN	2 (<0.1)	2 (<0.1)
With total bilirubin ≥2x ULN[1]	5 (0.1)	4 (0.1)
Alkaline phosphatase <2x ULN[2]	2 (<0.1)	4 (0.1)
Alkaline phosphatase ≥2x ULN[2]	3 (0.1)	0

1 Total bilirubin elevation within 30 days after ALT and/or AST elevation

2 Maximum alkaline phosphatase value within 30 days after ALT and/or AST elevation

Source data: [SCS appendix 2, c35146126, Table 2.3.1.2]

Hepatic events (occurring up to 30 days after treatment discontinuation) were adjudicated; adjudication results with patient details are summarised in the CTRs. No hepatic events that met the criteria for adjudication were reported in trials 1245.168 and 1245.148.

Ketoacidosis

For a comprehensive analysis, ketoacidosis was investigated using both broad and narrow BIcMQs. Based on the broad BIcMQ, events suggestive of ketoacidosis were reported for 63 patients (1.2%) in the empagliflozin group and for 77 patients (1.5%) in the placebo group; see Table 31. . Metabolic acidosis was the most frequent PT of the broad BIcMQ; there was no relevant increase in frequency with empagliflozin treatment.

All events in the broad BIcMQ were adjudicated (except for the PTs 'abnormal blood bicarbonate' and 'decreased blood bicarbonate' in trial 1245.110, which were added to the broad BIcMQ as part of a MedDRA update while the trial was ongoing). One patient in each group had an event which was adjudicated as certain ketoacidosis by the independent CEC (both patients had T2DM at baseline). The event was of mild severity in the patient treated with empagliflozin and of moderate severity in the patient treated with placebo.

The narrow BIcMQ ketoacidosis included 4 patients (0.1%) in the empagliflozin group and 6 patients (0.1%) in the placebo group. Subgroups (by diabetes status and sex) and ketoacidosis leading to discontinuation of study medication were analysed based on the narrow BIcMQ (Table 31.)

Table 31. Patients with ketoacidosis (BIcMQ; frequency ≥0.1% in at least one treatment group at the PT level) in SAF-HF1 – TS

MedDRA PT	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Ketoacidosis (broad BIcMQ)	77 (1.5)	0.97	63 (1.2)	0.79
Metabolic acidosis	23 (0.4)	0.29	24 (0.5)	0.30
Diabetic metabolic decompensation	25 (0.5)	0.31	13 (0.2)	0.16
Blood bicarbonate decreased	19 (0.4)	0.24	18 (0.3)	0.23
Ketoacidosis	3 (0.1)	0.04	1 (<0.1)	0.01
Ketosis	3 (0.1)	0.04	0	0
Diabetic ketoacidosis	2 (<0.1)	0.03	3 (0.1)	0.04
Ketoacidosis (broad BIcMQ), serious	47 (0.9)	0.59	29 (0.6)	0.36
Ketoacidosis (narrow BIcMQ)	6 (0.1)	0.08	4 (0.1)	0.05
With T2DM	5/2574 (0.2)	0.13	4/2565 (0.2)	0.10
With pre-diabetes	1/1708 (0.1)	0.04	0/1729	0

For subgroups, patients in subgroup with events/all patients in subgroup (%) are shown. There were no patients with events in the 'T1DM' and 'Without diabetes or pre-diabetes' categories.

Source data: [SCS appendix 2, c35146126, Tables 2.2.3.4 to 6, 2.2.3.9]

AEs leading to lower limb amputation (LLA)

These events were only analysed for trials with a duration of longer than 12 weeks (i.e. 1245.110 and 1245.121). The frequencies of patients with investigator-defined AEs leading to LLA up to trial completion were similar in the empagliflozin group (29 patients, 0.6%) and in the placebo group (33 patients, 0.7%); see Table 27. . Amputations were mostly minor (e.g. toe[s]) rather than major (empagliflozin: 8 patients [0.2%], placebo: 7 patients [0.1%]; e.g. above the knee). Most common reasons for the first LLA were untreatable/necrotising infection and ischaemic reasons.

Investigator-defined AEs leading to LLA (reported as AESIs during the on-treatment period) were reported for 21 patients (0.4%) in the empagliflozin group and 23 patients (0.5%) in the placebo group.

Subgroups were analysed by baseline eGFR, diabetes status, presence of a previous amputation, and history of peripheral arterial occlusive disease. The results were consistent with the main analysis of AEs leading to LLA.

Urinary tract infection

The frequency of patients with urinary tract infection (narrow sub BIcMQ) was higher in the empagliflozin group than in the placebo group (Table 32.). The most frequently reported PT was urinary tract infection, which was mainly driving the difference between groups. Other PTs were reported with similar and/or low (≤0.2%) frequencies in both treatment groups.

A similar trend as for urinary tract infection (narrow BIcMQ) was observed for the frequencies of patients with complicated urinary tract infections and patients with urinary tract infections leading to treatment discontinuation (Table 32.).

Table 32. Patients with urinary tract infection (BIcMQ; frequency ≥0.1% in at least one treatment group at the PT level) in SAF-HF1 – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Urinary tract infection (narrow BIcMQ)	335 (6.4)	4.37	402 (7.7)	5.27
Urinary tract infection	259 (5.0)	3.35	314 (6.0)	4.07
Cystitis	61 (1.2)	0.77	51 (1.0)	0.64
Urosepsis	12 (0.2)	0.15	17 (0.3)	0.21
Escherichia urinary tract	4 (0.1)	0.05	8 (0.2)	0.10
Urethritis	4 (0.1)	0.05	8 (0.2)	0.10
Pyelonephritis	3 (0.1)	0.04	7 (0.1)	0.09
Pyelonephritis acute	5 (0.1)	0.06	7 (0.1)	0.09
Urinary tract infection bacterial	3 (0.1)	0.04	7 (0.1)	0.09
Asymptomatic bacteriuria	6 (0.1)	0.08	5 (0.1)	0.06
Complicated	62 (1.2)	0.78	78 (1.5)	0.98
Leading to discont. of study medication	21 (0.4)	0.26	34 (0.7)	0.42

Source data: [SCS appendix 2, c35146126, Tables 2.2.5.4 to 6]

Subgroup analyses were performed by age, sex, race, and baseline eGFR, diabetes status, and history of chronic or recurrent urinary tract infection. The results of the subgroup analyses were generally similar to the main analyses of urinary tract infections.

Investigator-defined urinary tract infections (including urosepsis and acute pyelonephritis) were reported for 403 patients (7.7%) in the empagliflozin group and 338 patients (6.5%) in the placebo group. Urinary tract infections were predominantly infections of the lower urinary tract (bladder and below) or asymptomatic bacteriuria. Most patients in both treatment groups had a single episode rather than multiple episodes of urinary tract infection.

The trend observed in the analysis, including the PT urosepsis and pyelonephritis based on the narrow sub BIcMQ (empagliflozin: 30 patients [0.6%], placebo: 21 patients [0.4%]; Table 33.) was similar to what was observed for urinary tract infection (narrow BIcMQ; presented above). Subgroup analyses by sex and diabetes status were performed for the PT urosepsis and pyelonephritis (narrow sub BIcMQ). The results showed an imbalance in female patients with urosepsis or pyelonephritis, with a higher frequency in the empagliflozin group than in the placebo group, and that events occurred in both patients with diabetes and patients without diabetes (Table 33.).

Table 33. Patients with acute pyelonephritis or urosepsis in SAF-HF1 – TS

MedDRA PT	Placebo	Empa 10 mg

	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Urosepsis (PT) or pyelonephritis (narrow sub BIcMQ)	21 (0.4)	0.26	30 (0.6)	0.38
Urosepsis	12 (0.2)	0.15	17 (0.3)	0.21
Pyelonephritis	3 (0.1)	0.04	7 (0.1)	0.09
Pyelonephritis acute	5 (0.1)	0.06	7 (0.1)	0.09
Pyelitis	2 (<0.1)	0.03	0	0
Kidney infection	0	0	2 (<0.1)	0.02
Male	15/3287 (0.5)	0.31	10/3311 (0.3)	0.20
Female	6/1915 (0.3)	0.20	20/1895 (1.1)	0.65
With diabetes	13/2579 (0.5)	0.33	15/2570 (0.6)	0.38
Without diabetes	8/2620 (0.3)	0.20	15/2633 (0.6)	0.37

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

Source data: [SCS appendix 2, c35146126, Tables 2.2.6.1 to 3]

Events of investigator-defined sepsis with source urinary tract infection or non-urinary tract infection were collected only in trials 1245.110, 1245.121, and 1245.148. Sepsis with an origin other than urinary tract infections (investigator-defined) was reported for 76 patients (1.6%) in the empagliflozin group and for 56 patients (1.1%) in the placebo group. The two EMPEROR trials contributed differently to the analysis of the pooled safety data (see below). No events were reported in trial 1245.148.

In trial 1245.121, sepsis with an origin other than urinary tract infections (investigator-defined, including those with missing origin) was reported for 28 patients (1.5%) in the empagliflozin group and for 14 patients (0.8%) in the placebo group. The difference in frequency could not be attributed to specific PTs. All cases were medically reviewed, and no clear pattern regarding the source of non-urinary tract infection sepsis could be observed. In trial 1245.110, the frequencies of patients with sepsis with an origin other than urinary tract infections (investigator-defined) were balanced between treatment groups (empagliflozin: 48 patients [1.6%], placebo: 43 patients [1.4%]).

Genital infection

Genital infections (based on narrow BIcMQ) were reported for more patients in the empagliflozin group than in the placebo group (Table 34.). The most frequent PTs in the empagliflozin group were vulvovaginal mycotic and vulvovaginal candidiasis. Genital infections leading to treatment discontinuation were infrequent, although they showed the same trend. No difference between treatment groups was observed in the frequencies of patients with complicated genital infections (Table 34.).

Table 34. Patients with genital infection (BIcMQ; frequency ≥0.2% in at least one treatment group at the PT level) in SAF-HF1 – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Genital infection (narrow BIcMQ)	35 (0.7)	0.44	101 (1.9)	1.28
Vulvovaginal mycotic	4 (0.1)	0.05	15 (0.3)	0.19

Vulvovaginal candidiasis	7 (0.1)	0.09	14 (0.3)	0.18
Genital infection fungal	0	0	11 (0.2)	0.14
Fungal balanitis	0	0	10 (0.2)	0.13
Balanoposthitis	0	0	9 (0.2)	0.11
Complicated	14 (0.3)	0.18	14 (0.3)	0.18
Leading to discont. of study medication	2 (<0.1)	0.03	15 (0.3)	0.19

Source data: [SCS appendix 2, c35146126, Tables 2.2.7.4 to 6]

Subgroup analyses were performed by age, sex, race, and baseline eGFR, diabetes status, and history of chronic or recurrent genital infection. The results of the subgroup analyses were consistent with the main analysis, showing higher frequencies in the empagliflozin group than in the placebo group (Table 35.).

Table 35. Patients with genital infection (BIcMQ) in subgroups in SAF-HF1 (by sex and diabetes status) – TS

Subgroup	Placebo		Empa 10 mg	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
All patients	35/5202 (0.7)	0.44	101/5206 (1.9)	1.28
Male	15/3287 (0.5)	0.31	53/3311 (1.6)	1.09
Female	20/1915 (1.0)	0.66	48/1895 (2.5)	1.59
With diabetes	19/2579 (0.7)	0.49	57/2570 (2.2)	1.48
Without diabetes	16/2620 (0.6)	0.40	44/2633 (1.7)	1.09

N, all patients in subgroup; n, patients in subgroup with analysed AE category

Source data: [SCS appendix 2, c35146126, Tables 2.2.7.4, 2.2.7.8, 2.2.7.11]

Investigator-defined genital infections were reported for 115 patients (2.2%) in the empagliflozin group and 32 patients (0.6%) in the placebo group. Most patients with genital infections had a single episode rather than multiple episodes.

Volume depletion and hypotension

The frequency of patients with volume depletion (narrow BIcMQ), including hypotension (BIcMQ, subset of volume depletion), was higher in the empagliflozin group than in the placebo group (Table 36.). The most frequently reported PT was hypotension, which was also analysed separately as BIcMQ. Hypotension based on the BIcMQ was reported for 499 patients (9.6%) in the empagliflozin group and for 430 patients (8.3%) in the placebo group. In the BIcMQ analysis, there was no other PT which predominantly accounted for the difference in frequencies. The same trend as in the analysis of all events was observed in the analysis of volume depletion (narrow BIcMQ) or hypotension (BIcMQ) leading to treatment discontinuation (which were infrequent) and in the analysis of serious volume depletion (narrow BIcMQ) or serious hypotension (BIcMQ; Table 36.).

Table 36. Patients with volume depletion (narrow BIcMQ) and hypotension (BIcMQ) in SAF-HF1 (frequency ≥0.2% in at least one treatment group at the PT level) – TS

MedDRA PT	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Volume depletion (narrow BIcMQ)	483 (9.3)	6.44	566 (10.9)	7.59
Dehydration	71 (1.4)	0.90	87 (1.7)	1.10
Hypovolaemia	8 (0.2)	0.10	6 (0.1)	0.07
Hypotension (BIcMQ, subset of vol. depletion)	430 (8.3)	5.69	499 (9.6)	6.64

Hypotension	313 (6.0)	4.09	372 (7.1)	4.87
Orthostatic hypotension	32 (0.6)	0.40	37 (0.7)	0.46
Circulatory collapse	10 (0.2)	0.13	3 (0.1)	0.04
Syncope	81 (1.6)	1.03	98 (1.9)	1.24
Presyncope	13 (0.2)	0.16	22 (0.4)	0.28
Volume depletion (narrow BIcMQ), serious	91 (1.7)	1.15	113 (2.2)	1.43
Hypotension (BIcMQ), serious	77 (1.5)	0.97	101 (1.9)	1.27
Volume depletion (narrow BIcMQ) leading to discont. of study medication	17 (0.3)	0.21	30 (0.6)	0.37
Hypotension (BIcMQ) leading to discont. of study medication	15 (0.3)	0.19	25 (0.5)	0.31

Source data: [SCS appendix 2, c35146126, Tables 2.2.8.2 to 4, 2.2.9.6 to 8]

Subgroup analyses for hypotension (BIcMQ) were performed by age, sex, race, baseline eGFR, diabetes status, blood pressure, and use of certain medications. The results of the subgroup analyses were consistent with the main analysis of hypotension.

The results of the subgroup analyses for volume depletion (narrow BIcMQ; by age, sex, race, baseline eGFR, diabetes status, blood pressure, and use of certain medications) were consistent with the results of the main analysis of volume depletion and with those for hypotension.

The analysis of clinically relevant investigator-defined symptomatic hypotension events (Table 37.) showed the same trend as the analysis of hypotension (BIcMQ) presented above.

Table 37. Patients with investigator-defined symptomatic hypotension events in SAF-HF1 – TS

	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5166 (100.0)		5171 (100.0)	
Patients with investigator-defined symptomatic hypotension events	262 (5.1)	3.40	309 (6.0)	4.02
Serious events	43 (0.8)	0.54	49 (0.9)	0.62
Leading to discontinuation	12 (0.2)	0.15	17 (0.3)	0.21

Investigator-defined symptomatic hypotension events were only collected for 1245.110, 1245.121, 1245.167, and 1245.168

Source data: [SCS appendix 2, c35146126, Tables 2.2.9.1, 2.2.9.3, 2.2.9.4]

In cases of symptomatic hypotension episodes, the intensity of both diuretic and non-diuretic anti-hypertensive therapy was more often reduced in the empagliflozin group than in the placebo group (Table 38.).

Table 38. Investigator-defined symptomatic hypotension episodes in SAF-HF1 - TS

	Placebo	Empa 10 mg
Number of patients, N	5166	5171
Number of episodes (episodes per 100 patient years at risk)	300 (3.77)	364 (4.55)
Intensity of diuretic therapy reduced	104 (1.31)	158 (1.98)
Intensity of non-diuretic anti-hypertensive therapy reduced	170 (2.14)	221 (2.76)

Investigator-defined symptomatic hypotension events were only collected for 1245.110, 1245.121, 1245.167, and 1245.168

Source data: [SCS appendix 2, c35146126, Table 2.2.9.5]

Hypoglycaemia

The frequencies of patients with confirmed hypoglycaemic events were balanced between treatment groups (Table 27.). No imbalance in confirmed hypoglycaemic events was observed in the subgroup analysis by diabetes status. The remaining subgroup analyses (i.e. by age, sex, race, and baseline eGFR) also showed no relevant difference between treatment groups.

Consistent results were obtained for the SMQ-based analysis: 124 patients (2.4%) in the empagliflozin group and 134 patients (2.6%) in the placebo group had hypoglycaemic events based on the narrow SMQ.

Investigator-defined hypoglycaemic events were reported for 122 patients (2.3%) in the empagliflozin group and 132 patients (2.5%) in the placebo group. Of those patients, similar proportions in both groups had hypoglycaemic events that required assistance (empagliflozin: 30 patients [0.6%], placebo: 28 patients [0.5%]). Most patients had 1 or 2 confirmed hypoglycaemic episodes rather than ≥3 episodes). The severity of hypoglycaemic AEs (investigator-defined) was summarised by diabetes status. The proportions of patients with severe hypoglycaemic events that required assistance were similar between treatment groups, and the events occurred predominantly in patients with T2DM (empagliflozin: 28 patients [1.1%], placebo: 26 patients [1.0%]) rather than in patients with pre-diabetes (empagliflozin: 1 patient [0.1%], placebo: 2 patients [0.1%]) or in patients without (pre-) diabetes (empagliflozin: 1 patient [0.1%], placebo: none).

Symptomatic hypoglycaemic episodes with a blood glucose level <54 mg/dL and no assistance required were less frequently reported in the empagliflozin group (32 episodes, 0.40 episodes/100 pt-yrs) than in the placebo group (128 episodes, 1.61 episodes/100 pt-yrs). For other categories of symptomatic or asymptomatic hypoglycaemic episodes, there was no marked imbalance in the frequencies between treatment groups.

Bone fracture

The frequencies of patients with bone fracture (BIcMQ) were similar between treatment groups (Table 39.). No relevant difference between treatment groups was observed for bone fractures leading to discontinuation, or reported as SAEs, or when including the events up to trial completion (Table 27.). There were no relevant differences between treatment groups in subgroup analyses by age, sex, race, baseline eGFR, and diabetes status.

Investigator-defined bone fractures were reported for 179 patients (3.4%) in the empagliflozin group and for 171 patients (3.3%) in the placebo group. Bone fractures were more frequently classified as traumatic rather than as non-traumatic (Table 39.).

Table 39. Patients with investigator-defined bone fracture in SAF-HF1 – TS

	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Patients with investigator-defined bone fracture	171 (3.3)	2.19	179 (3.4)	2.28
Traumatic	155 (3.0)	1.99	156 (3.0)	1.98
Non-traumatic	15 (0.3)	0.19	26 (0.5)	0.33

Source data: [SCS appendix 2, c35146126, Tables 2.2.11.1 to 3]

Urinary tract malignancy

The frequencies of patients with urinary tract malignancies (broad sub BIcMQs) were similar between the empagliflozin group (18 patients, 0.4%) and the placebo group (14 patients, 0.3%; Table 27.) in patients with a cumulative exposure of ≥6 months when events up to trial completion were considered. Consistent results were obtained for the overall population regardless of exposure (empagliflozin: 28 patients [0.5%], placebo: 22 patients [0.4%]; analysis also considered events up to trial completion; Table 27.).

Constipation

In SAF-HF1, the PT constipation was reported for more patients in the empagliflozin group (153 patients, 2.9%) than in the placebo group (107 patients, 2.1%). Few patients had serious events or events leading to treatment discontinuation (Table 40.). The trend was generally observed in both EMPEROR trials and across all subgroups, including by diabetes status.

Table 40. Patients with the PT constipation in SAF-HF1 and in trials 1245.110 and 1245.121 – TS

	SAF-HF1				**Trial 1245.110 (EMPEROR-Preserved)**				**Trial 1245.121 (EMPEROR-Reduced)**			
	Placebo		Empa 10 mg		Placebo		Empa 10 mg		Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)		2989 (100.0)		2996 (100.0)		1863 (100.0)		1863 (100.0)	
PT constipation	107 (2.1)	1.36	153 (2.9)	1.94	76 (2.5)	1.37	93 (3.1)	1.67	27 (1.4)	1.21	57 (3.1)	2.56
Investigator defined drug-related	7 (0.1)	0.09	13 (0.2)	0.16	6 (0.2)	0.11	8 (0.3)	0.14	1 (0.1)	0.04	5 (0.3)	0.22
Leading to treatment discont.	1 (<0.1)	0.01	2 (<0.1)	0.02	1 (<0.1)	0.02	0		0		2 (0.1)	0.09
Serious	2 (<0.1)	0.03	4 (0.1)	0.05	1 (<0.1)	0.02	1 (<0.1)	0.02	1 (0.1)	0.04	3 (0.2)	0.13

Source data: [SCS appendix 2, c35146126, Tables 2.1.1.2, 5 to 7; CTR 1245.110, c31803238, Tables 15.3.1.1: 2, 5 to 7; CTR 1245.121, c28576542, Tables 15.3.1.1: 2, 5 to 7]

Unexpected AEs

Fall

Previously, in trial 1245.121 (EMPEROR-Reduced), the PT fall was reported for more patients in the empagliflozin group than in the placebo group. However, this imbalance was not observed in trial 1245.110 (EMPEROR-Preserved). When all 5 trials in patients with HF were pooled in SAF-HF1, the EMPEROR trials contributed almost all events of fall, and no obvious imbalance in fall was observed (Table 41.).

Table 41. Patients with the PT fall in SAFHF1 and in trials 1245.110 and 1245.121 – TS

	SAF-HF1				**Trial 1245.110 (EMPEROR-Preserved)**				**Trial 1245.121 (EMPEROR-Reduced)**			
	Placebo		Empa 10 mg		Placebo		Empa 10 mg		Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)		2989 (100.0)		2996 (100.0)		1863 (100.0)		1863 (100.0)	
PT fall	249 (4.8)	3.24	261 (5.0)	3.37	219 (7.3)	4.08	213 (7.1)	3.92	27 (1.4)	1.21	43 (2.3)	1.92
Investigator defined drug-related	4 (0.1)	0.05	3 (0.1)	0.04	3 (0.1)	0.05	3 (0.1)	0.05	1 (0.1)	0.04	0	
Leading to treatment discont.	3 (0.1)	0.04	3 (0.1)	0.04	2 (0.1)	0.04	1 (<0.1)	0.02	1 (0.1)	0.04	2 (0.1)	0.09
Serious	35 (0.7)	0.44	47 (0.9)	0.59	30 (1.0)	0.54	31 (1.0)	0.55	4 (0.2)	0.18	15 (0.8)	0.66

Source data: [SCS appendix 2, c35146126, Tables 2.1.1.2, 5 to 7; CTR 1245.110, c31803238, Tables 15.3.1.1: 2, 5 to 7; CTR 1245.121, c28576542, Tables 15.3.1.1: 2, 5 to 7]

Considering the late divergence in falls between treatment groups (after about 8 months in trial 1245.121), the lack of a plausible pathophysiological cause related to empagliflozin's mode of action (e.g. via hypotension, volume depletion, hypoglycaemia), and the lack of consistency between the clinical trial results (of trials 1245.121 and 1245.25), the small numerical imbalance in the PT fall observed in trial 1245.121 was likely due to random variation associated with a large number of comparisons between treatment groups in the safety analyses.

No obvious pattern in the PT fall was observed in the subgroup analyses of the EMPEROR trials. Numerically more patients in the empagliflozin group than in the placebo group experienced fall in the Asian subgroup in both trials, while in the White and Black/African American subgroups of trial 1245.110, the trend was opposite with fewer patients in the empagliflozin group than in the placebo group (Table 42.).

Table 42. Subgroup analysis by race for the PT fall in trials 1245.110 and 1245.121 – TS

	Trial 1245.110 (EMPEROR-Preserved)				**Trial 1245.121 (EMPEROR-Reduced)**			
	Placebo		Empa 10 mg		Placebo		Empa 10 mg	
	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs	n/N (%)	Rate/100 pt-yrs
All	219/2989 (7.3)	4.08	213/2996 (7.1)	3.92	27/1863 (1.4)	1.21	43/1863 (2.3)	1.92
White	173/2254 (7.7)	4.31	162/2285 (7.1)	3.92	24/1301 (1.8)	1.56	33/1325 (2.5)	2.11
Black/African American	10/125 (8.0)	4.85	7/133 (5.3)	3.01	1/134 (0.7)	0.64	4/123 (3.3)	2.71
Asian	26/411 (6.3)	3.31	39/413 (9.4)	5.06	1/334 (0.3)	0.23	6/337 (1.8)	1.36
Other including mixed race	10/198 (5.1)	2.79	5/164 (3.0)	1.69	0/63		0 /51	

Source data: [CTR 1245.110, c31803238, Tables 15.3.1.2.2: 5, 15.3.1.1: 2; CTR 1245.121, c28576542, Tables 15.3.1.2.2: 5, 15.3.1.1: 2]

In Asian patients, no event led to treatment discontinuation and serious events were infrequent (Table 43.).

Table 43. Asian patients with the PT fall in trials 1245.110 and 1245.121 – TS

	Trial 1245.110 (EMPEROR-Preserved)				**Trial 1245.121 (EMPEROR-Reduced)**			
	Placebo		Empa 10 mg		Placebo		Empa 10 mg	
	N (%)	Rate/ 100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of Asian patients	411 (100.0)		413 (100.0)		334 (100.0)		337 (100.0)	
PT fall	26 (6.3)	3.31	39 (9.4)	5.06	1 (0.3)	0.23	6 (1.8)	1.36
Leading to treatment discontinuation	0		0		0		0	
Serious	4 (1.0)	0.50	8 (1.9)	1.00	0		1 (0.3)	0.23

Source data: [CTR 1245.110, c31803238, Tables 15.3.1.2.2: 5, 15.3.1.2.3: 5, 15.3.1.2.4: 5; CTR 1245.121, c28576542, Tables 15.3.1.2.2: 5, 15.3.1.2.3: 5, 15.3.1.2.4: 5]

In addition, each event of fall in the Asian patients of trial 1245.110 was extensively medically reviewed for the origin of the fall. The incidence of fall started to diverge between treatment groups after about 1 year. No plausible pathophysiological cause related to empagliflozin's mode of action (e.g. via hypotension, volume depletion, hypoglycaemia) could be identified. The imbalance appeared to be mainly due to accidental falls, i.e. reported by the investigator as "accidental fall" or "mechanical fall" which implied an external force (e.g. environmental) or due to other causes (e.g. "slipped", "stumbled", etc.).

In conclusion, considering the late divergence in falls between treatment groups, the lack of a plausible pathophysiological cause related to empagliflozin's mode of action, and the lack of consistency in other subgroups (including other races), the small numerical imbalance in the PT fall observed in Asian patients was likely due to random variation associated with a large number of comparisons between treatment groups and among subgroups in the safety analyses.

Serious adverse event/deaths/other significant events

The overall frequency of patients with SAEs was lower in the empagliflozin group than in the placebo group. Serious adverse events were most commonly reported in the SOC cardiac disorders. On the PT level, cardiac failure, pneumonia, acute kidney injury, atrial fibrillation, and cardiac failure congestive were most common. All other SAEs by PT were reported for <2.0% of patients in either group (Table 44.).

In addition, all-cause and HF-related hospitalisations and all-cause mortality were analysed as efficacy endpoints in the two EMPEROR trials. In both trials, the risks of heart failure hospitalisations, recurrent heart failure hospitalisations, and investigator-defined CV hospitalisations were reduced with empagliflozin treatment compared with placebo. Also, in both trials, the cause of each death was adjudicated by the CEC, and the incidences of all-cause mortality were similar between treatment groups.

Table 44. Patients with SAEs in SAF-HF1 (frequency ≥1.0% in at least one 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 patients	5202 (100.0)		5206 (100.0)	
Total with SAEs	2502 (48.1)	44.39	2250 (43.2)	37.35
Cardiac disorders	1552 (29.8)	23.67	1259 (24.2)	18.14
Cardiac failure	1064 (20.5)	15.18	792 (15.2)	10.74
Atrial fibrillation	127 (2.4)	1.62	118 (2.3)	1.50
Cardiac failure congestive	110 (2.1)	1.40	83 (1.6)	1.05
Ventricular tachycardia	60 (1.2)	0.76	77 (1.5)	0.97
Acute myocardial infarction	66 (1.3)	0.83	75 (1.4)	0.94
Cardiac failure chronic	62 (1.2)	0.78	43 (0.8)	0.54
Cardiac failure acute	58 (1.1)	0.73	32 (0.6)	0.40
Myocardial infarction	44 (0.8)	0.55	53 (1.0)	0.67
Infections and infestations	501 (9.6)	6.59	475 (9.1)	6.17
Pneumonia	182 (3.5)	2.32	155 (3.0)	1.96
COVID-19	50 (1.0)	0.63	50 (1.0)	0.63
Urinary tract infection	40 (0.8)	0.50	50 (1.0)	0.63
Nervous system disorders	264 (5.1)	3.40	299 (5.7)	3.83
Ischaemic stroke	55 (1.1)	0.69	61 (1.2)	0.77
Renal and urinary disorders	315 (6.1)	4.06	241 (4.6)	3.07
Acute kidney injury	166 (3.2)	2.11	118 (2.3)	1.49
Renal impairment	69 (1.3)	0.87	55 (1.1)	0.69
Respiratory, thoracic and mediastinal disorders	220 (4.2)	2.82	160 (3.1)	2.03
Chronic obstructive pulmonary disease	50 (1.0)	0.63	34 (0.7)	0.43
General disorders and administration site conditions	175 (3.4)	2.22	172 (3.3)	2.16
Death[1]	65 (1.2)	0.82	76 (1.5)	0.95

1 Deaths not attributed to another PT by the investigator. The frequencies of patients with fatal AEs were balanced between treatment groups (see **Error! Reference source not found.**)

Source data: [SCS appendix 2, c35146126, Table 2.1.1.7]

Laboratory findings

A summary of patients with elevated serum creatinine in SAF-HF1 is provided above (Decreased renal function). Renal function parameters were also analysed as efficacy endpoints in the long-term outcome trials. A summary of patients with elevated liver enzymes in SAF-HF1 is also provided above (Hepatic injury).

Safety laboratory analyses at trial level are presented in CTRs. In trials 1245.110 and 1245.121, haemoglobin and haematocrit values increased on treatment and then partially returned to baseline after treatment discontinuation in the empagliflozin group, with small decreases observed in the placebo group. There was a decrease in uric acid (urate) values in the empagliflozin group compared with the placebo group. After treatment discontinuation, uric acid values returned towards baseline in the empagliflozin group. There were no relevant alterations in the other safety laboratory parameters. In the 12-week trials, the trends were consistent with those observed in 1245.110 and 1245.121.

Vital sign, physical findings and other observation related to safety

No meaningful changes in blood pressure (systolic or diastolic) or in heart/pulse rate were observed with empagliflozin treatment compared with placebo in any of the HF trials. There were no relevant differences

in new ECG findings after baseline between empagliflozin and placebo. No pregnancy was reported other than a spontaneous abortion as an AE in trial 1245.121.

Safety in special populations

Subgroup analyses of AEs were carried out by demographic and baseline characteristics (age, sex, race, geographic region, ethnicity, diabetes status at baseline, baseline eGFR, baseline blood pressure, and baseline use of ACE-inhibitor/ARB/ARNi, diuretics, or loop/high-ceiling diuretics).

In SAF-HF1, the AE profile in subgroups was generally consistent with that of the overall population, including the subgroups by diabetes status and by eGFR categories at baseline (including patients with an eGFR of <30 mL/min/1.73 m^2). No relevant difference in the AE profile was observed between patients with HFrEF and patients with HFpEF.

Age

Adverse events by age categories were generally consistent with the overall AE profile of the pooled safety data (Table 45.).

Table 45. AEs by age in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Age <50 years	244 (100.0)		198 (100.0)	
Any AE	188 (77.0)	158.71	147 (74.2)	140.93
Leading to discont. of study medication	28 (11.5)	8.52	25 (12.6)	8.94
SAEs	101 (41.4)	43.04	72 (36.4)	32.78
Acute renal failure (SMQ)	18 (7.4)	5.71	15 (7.6)	5.53
Urinary tract infection (BIcMQ)	12 (4.9)	3.75	6 (3.0)	2.21
Genital infection (BIcMQ)	6 (2.5)	1.84	5 (2.5)	1.82
Volume depletion (BIcMQ)	22 (9.0)	7.14	17 (8.6)	6.38
Hypotension (BIcMQ)	20 (8.2)	6.48	15 (7.6)	5.60
Confirmed hypoglycaemic events[1]	5 (2.0)	1.55	0	0
Bone fracture (BIcMQ)	3 (1.2)	0.91	1 (0.5)	0.36
Age 50 to <65 years	1178 (100.0)		1154 (100.0)	
Any AE	917 (77.8)	149.31	869 (75.3)	124.81
Leading to discont. of study medication	185 (15.7)	10.66	160 (13.9)	9.44
SAEs	530 (45.0)	41.84	445 (38.6)	34.26
Acute renal failure (SMQ)	133 (11.3)	8.09	104 (9.0)	6.45
Urinary tract infection (BIcMQ)	49 (4.2)	2.90	63 (5.5)	3.82
Genital infection (BIcMQ)	8 (0.7)	0.46	19 (1.6)	1.13
Volume depletion (BIcMQ)	85 (7.2)	5.13	97 (8.4)	6.00
Hypotension (BIcMQ)	77 (6.5)	4.61	95 (8.2)	5.87
Confirmed hypoglycaemic events[1]	29 (2.5)	1.69	25 (2.2)	1.49
Bone fracture (BIcMQ)	22 (1.9)	1.28	20 (1.7)	1.19
Age 65 to <75 years	1852 (100.0)		1932 (100.0)	
Any AE	1493 (80.6)	144.16	1537 (79.6)	137.81
Leading to discont. of study medication	291 (15.7)	10.06	322 (16.7)	10.76
SAEs	853 (46.1)	40.22	818 (42.3)	35.61

Acute renal failure (SMQ)	211 (11.4)	7.73	209 (10.8)	7.35
Urinary tract infection (BIcMQ)	117 (6.3)	4.18	133 (6.9)	4.60
Genital infection (BIcMQ)	10 (0.5)	0.34	32 (1.7)	1.07
Volume depletion (BIcMQ)	147 (7.9)	5.30	203 (10.5)	7.23
Hypotension (BIcMQ)	135 (7.3)	4.85	178 (9.2)	6.30
Confirmed hypoglycaemic events[1]	32 (1.7)	1.11	38 (2.0)	1.28
Bone fracture (BIcMQ)	49 (2.6)	1.71	69 (3.6)	2.35

Continued on the next page

AEs by age in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Age 75 to <85 years	1653 (100.0)		1675 (100.0)	
Any AE	1406 (85.1)	180.04	1398 (83.5)	157.45
Leading to discont. of study medication	326 (19.7)	12.72	345 (20.6)	13.26
SAEs	870 (52.6)	49.94	777 (46.4)	40.13
Acute renal failure (SMQ)	188 (11.4)	7.70	188 (11.2)	7.72
Urinary tract infection (BIcMQ)	117 (7.1)	4.70	166 (9.9)	6.73
Genital infection (BIcMQ)	11 (0.7)	0.43	43 (2.6)	1.67
Volume depletion (BIcMQ)	196 (11.9)	8.19	212 (12.7)	8.73
Hypotension (BIcMQ)	172 (10.4)	7.12	178 (10.6)	7.25
Confirmed hypoglycaemic events[1]	39 (2.4)	1.54	35 (2.1)	1.35
Bone fracture (BIcMQ)	79 (4.8)	3.17	74 (4.4)	2.88
Age ≥85 years	275 (100.0)		247 (100.0)	
Any AE	230 (83.6)	172.59	213 (86.2)	195.01
Leading to discont. of study medication	69 (25.1)	17.55	60 (24.3)	15.82
SAEs	148 (53.8)	54.44	138 (55.9)	50.74
Acute renal failure (SMQ)	37 (13.5)	9.94	31 (12.6)	8.65
Urinary tract infection (BIcMQ)	40 (14.5)	10.98	34 (13.8)	9.63
Genital infection (BIcMQ)	0	0	2 (0.8)	0.52
Volume depletion (BIcMQ)	33 (12.0)	8.99	37 (15.0)	10.89
Hypotension (BIcMQ)	26 (9.5)	6.96	33 (13.4)	9.56
Confirmed hypoglycaemic events[1]	3 (1.1)	0.77	3 (1.2)	0.80
Bone fracture (BIcMQ)	18 (6.5)	4.74	18 (7.3)	4.91

1 Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or where assistance was required

Source data: [SCS appendix 2, c35146126, Tables 2.1.2.2.1, 2.1.2.3.1, 2.1.2.4.1, 2.2.20.1]

Diabetes status at baseline

Adverse events by diabetes status at baseline were generally consistent with the overall AE profile of the pooled safety data (Table 46.).

Table 46. AEs by baseline diabetes status in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
With diabetes	2579 (100.0)		2570 (100.0)	
Any AE	2121 (82.2)	167.66	2086 (81.2)	151.31
Leading to discont. of study medication	475 (18.4)	12.21	477 (18.6)	12.26
SAEs	1287 (49.9)	47.71	1158 (45.1)	39.84
Acute renal failure (SMQ)	324 (12.6)	8.83	332 (12.9)	9.16
Hepatic injury (SMQ)	137 (5.3)	3.61	113 (4.4)	2.95
Ketoacidosis (narrow BIcMQ)	5 (0.2)	0.13	4 (0.2)	0.10
AEs leading to LLA[1] (up to trial completion)	30/2397 (1.3)	0.68	27/2392 (1.1)	0.61
Urinary tract infection (BIcMQ)	184 (7.1)	4.91	208 (8.1)	5.59
Genital infection (BIcMQ)	19 (0.7)	0.49	57 (2.2)	1.48

Volume depletion (BIcMQ)	226 (8.8)	6.11	271 (10.5)	7.36
Hypotension (BIcMQ)	198 (7.7)	5.31	235 (9.1)	6.35
Confirmed hypoglycaemic events[2]	90 (3.5)	2.36	84 (3.3)	2.20
Bone fracture (BIcMQ)	81 (3.1)	2.11	89 (3.5)	2.32
Without diabetes	2620 (100.0)		2633 (100.0)	
Any AE	2112 (80.6)	149.08	2077 (78.9)	135.41
Leading to discont. of study medication	424 (16.2)	10.55	435 (16.5)	10.73
SAEs	1215 (46.4)	41.35	1092 (41.5)	35.04
Acute renal failure (SMQ)	263 (10.0)	6.86	215 (8.2)	5.52
Hepatic injury (SMQ)	111 (4.2)	2.81	84 (3.2)	2.10
Ketoacidosis (narrow BIcMQ)	1 (<0.1)	0.02	0	0
AEs leading to LLA[1] (up to trial completion)	3/2455 (0.1)	0.07	2/2467 (0.1)	0.04
Urinary tract infection (BIcMQ)	151 (5.8)	3.86	194 (7.4)	4.96
Genital infection (BIcMQ)	16 (0.6)	0.40	44 (1.7)	1.09
Volume depletion (BIcMQ)	257 (9.8)	6.76	294 (11.2)	7.79
Hypotension (BIcMQ)	232 (8.9)	6.07	263 (10.0)	6.90
Confirmed hypoglycaemic events[2]	18 (0.7)	0.45	17 (0.6)	0.42
Bone fracture (BIcMQ)	90 (3.4)	2.28	93 (3.5)	2.32

1 Data collected only in 1245.110 and 1245.121, shown as patients with events/patients in group (%)

2 Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or where assistance was required

Baseline eGFR

The adverse event profile in each eGFR category was generally consistent with the overall AE profile of the pooled safety data (Table 47.).

Table 47. AEs by baseline eGFR in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
eGFR ≥90 mL/min/1.73 m²	481 (100.0)		482 (100.0)	
Any AE	360 (74.8)	129.13	346 (71.8)	107.08
Leading to discont. of study medication	51 (10.6)	6.90	62 (12.9)	8.32
SAEs	188 (39.1)	32.99	163 (33.8)	27.36
Acute renal failure (SMQ)	25 (5.2)	3.46	20 (4.1)	2.71
AEs leading to LLA[1] (up to trial completion)	3/457 (0.7)	0.36	2/460 (0.4)	0.24
Urinary tract infection (BIcMQ)	26 (5.4)	3.66	25 (5.2)	3.47
Genital infection (BIcMQ)	5 (1.0)	0.68	7 (1.5)	0.95
Volume depletion (BIcMQ)	30 (6.2)	4.20	35 (7.3)	4.89
Hypotension (BIcMQ)	27 (5.6)	3.77	35 (7.3)	4.89
Confirmed hypoglycaemic events[2]	9 (1.9)	1.23	5 (1.0)	0.67
Bone fracture (BIcMQ)	10 (2.1)	1.36	12 (2.5)	1.63
eGFR 60 to <90 mL/min/1.73 m²	2139 (100.0)		2141 (100.0)	
Any AE	1693 (79.1)	138.32	1661 (77.6)	126.79
Leading to discont. of study medication	313 (14.6)	9.30	317 (14.8)	9.43
SAEs	945 (44.2)	37.84	817 (38.2)	30.87
Acute renal failure (SMQ)	170 (7.9)	5.24	150 (7.0)	4.62
AEs leading to LLA[1] (up to trial completion)	9/2006 (0.4)	0.24	9/2002 (0.4)	0.24
Urinary tract infection (BIcMQ)	106 (5.0)	3.22	145 (6.8)	4.47

Genital infection (BIcMQ)	14 (0.7)	0.42	49 (2.3)	1.47
Volume depletion (BIcMQ)	175 (8.2)	5.44	185 (8.6)	5.83
Hypotension (BIcMQ)	157 (7.3)	4.85	166 (7.8)	5.20
Confirmed hypoglycaemic events[2]	38 (1.8)	1.14	24 (1.1)	0.72
Bone fracture (BIcMQ)	56 (2.6)	1.69	67 (3.1)	2.03
eGFR 45 to <60 mL/min/1.73 m²	1326 (100.0)		1322 (100.0)	
Any AE	1091 (82.3)	159.68	1073 (81.2)	150.84
Leading to discont. of study medication	232 (17.5)	11.31	237 (17.9)	11.69
SAEs	655 (49.4)	45.06	609 (46.1)	40.26
Acute renal failure (SMQ)	152 (11.5)	7.84	139 (10.5)	7.26
AEs leading to LLA[1] (up to trial completion)	11/1238 (0.9)	0.48	8/1224 (0.7)	0.35
Urinary tract infection (BIcMQ)	81 (6.1)	4.10	110 (8.3)	5.70
Genital infection (BIcMQ)	9 (0.7)	0.44	23 (1.7)	1.14
Volume depletion (BIcMQ)	121 (9.1)	6.22	182 (13.8)	9.70
Hypotension (BIcMQ)	109 (8.2)	5.57	161 (12.2)	8.52
Confirmed hypoglycaemic events[2]	23 (1.7)	1.14	27 (2.0)	1.34
Bone fracture (BIcMQ)	48 (3.6)	2.39	47 (3.6)	2.36

Continued on the next page

AEs by baseline eGFR in SAF-HF1 – TS

Category of AEs	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
eGFR 30 to <45 mL/min/1.73 m²	980 (100.0)		977 (100.0)	
Any AE	848 (86.5)	211.84	826 (84.5)	175.16
Leading to discont. of study medication	210 (21.4)	14.78	212 (21.7)	14.74
SAEs	543 (55.4)	60.15	487 (49.8)	48.11
Acute renal failure (SMQ)	171 (17.4)	13.23	175 (17.9)	13.57
AEs leading to LLA[1] (up to trial completion)	8/898 (0.9)	0.48	6/909 (0.7)	0.36
Urinary tract infection (BIcMQ)	93 (9.5)	6.84	91 (9.3)	6.58
Genital infection (BIcMQ)	6 (0.6)	0.42	19 (1.9)	1.32
Volume depletion (BIcMQ)	122 (12.4)	9.33	117 (12.0)	8.64
Hypotension (BIcMQ)	108 (11.0)	8.18	101 (10.3)	7.37
Confirmed hypoglycaemic events[2]	22 (2.2)	1.55	24 (2.5)	1.68
Bone fracture (BIcMQ)	47 (4.8)	3.37	46 (4.7)	3.24
eGFR <30 mL/min/1.73 m²	273 (100.0)		283 (100.0)	
Any AE	240 (87.9)	253.80	258 (91.2)	269.67
Leading to discont. of study medication	92 (33.7)	27.61	84 (29.7)	22.37
SAEs	170 (62.3)	81.29	174 (61.5)	68.14
Acute renal failure (SMQ)	69 (25.3)	23.03	63 (22.3)	18.94
AEs leading to LLA[1] (up to trial completion)	2/250 (0.8)	0.49	4/263 (1.5)	0.87
Urinary tract infection (BIcMQ)	29 (10.6)	9.00	31 (11.0)	8.78
Genital infection (BIcMQ)	1 (0.4)	0.30	3 (1.1)	0.80
Volume depletion (BIcMQ)	35 (12.8)	11.09	47 (16.6)	13.94
Hypotension (BIcMQ)	29 (10.6)	9.01	36 (12.7)	10.48
Confirmed hypoglycaemic events[2]	16 (5.9)	4.94	21 (7.4)	5.77
Bone fracture (BIcMQ)	10 (3.7)	3.03	10 (3.5)	2.67

Patients with missing information are shown in the source tables; this includes 1 patient in the empagliflozin group and 3 patients in the placebo group.

1 Data collected only in 1245.110 and 1245.121, shown as patients with events/patients in group (%)

2 Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or where assistance was required

Source data: [SCS, c35218777, Section 5.1.6]

Use in pregnancy and lactation

The use of empagliflozin during pregnancy and lactation was not specifically studied in the HF trials. See the currently approved product information of empagliflozin for more information.

A spontaneous abortion was reported as an AE in trial 1245.121. No pregnancies were reported in trials 1245.168, 1245.167, 1245.148, or 1245.110.

Safety related to drug-drug interactions and other interactions

Drug interactions were not specifically studied in the HF trials. See the currently approved product information of empagliflozin for more information. For subgroup analyses by certain medications (i.e. ACE-inhibitors/ARB/ARNi, diuretics, loop/high-ceiling diuretics) at baseline, see below.

Baseline use of certain medications

Only acute renal failure (SMQ), volume depletion (BIcMQ), and hypotension (BIcMQ, subset of volume depletion) were included in subgroup analyses. Adverse events by baseline use of certain medications (i.e. ACE-inhibitors/ARB/ARNi, diuretics, loop/high-ceiling diuretics) showed trends similar to those observed for the overall population (Table 48.).

Table 48. AEs by baseline use of certain medications in SAF-HF1 – TS

Category of AEs	Placebo		Empa 10 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Without ACE-inhibitor, ARB or ARNi	856 (100.0)		851 (100.0)	
Acute renal failure (SMQ)	97 (11.3)	7.81	87 (10.2)	6.72
Volume depletion (BIcMQ)	83 (9.7)	6.79	90 (10.6)	7.04
Hypotension (BIcMQ)	75 (8.8)	6.09	80 (9.4)	6.20
With ACE-inhibitor, ARB or ARNi	4346 (100.0)		4355 (100.0)	
Acute renal failure (SMQ)	490 (11.3)	7.83	460 (10.6)	7.39
Volume depletion (BIcMQ)	400 (9.2)	6.37	476 (10.9)	7.70
Hypotension (BIcMQ)	355 (8.2)	5.62	419 (9.6)	6.73
Without ARNi	4684 (100.0)		4732 (100.0)	
Acute renal failure (SMQ)	530 (11.3)	7.61	509 (10.8)	7.23
Volume depletion (BIcMQ)	432 (9.2)	6.20	503 (10.6)	7.19
Hypotension (BIcMQ)	380 (8.1)	5.41	445 (9.4)	6.32
With ARNi	518 (100.0)		474 (100.0)	
Acute renal failure (SMQ)	57 (11.0)	10.61	38 (8.0)	7.86
Volume depletion (BIcMQ)	51 (9.8)	9.64	63 (13.3)	13.52
Hypotension (BIcMQ)	50 (9.7)	9.42	54 (11.4)	11.45
Without diuretics	510 (100.0)		579 (100.0)	
Acute renal failure (SMQ)	45 (8.8)	5.51	37 (6.4)	4.03
Volume depletion (BIcMQ)	30 (5.9)	3.69	40 (6.9)	4.37
Hypotension (BIcMQ)	27 (5.3)	3.30	34 (5.9)	3.70
With diuretics	4692 (100.0)		4627 (100.0)	
Acute renal failure (SMQ)	542 (11.6)	8.11	510 (11.0)	7.72
Volume depletion (BIcMQ)	453 (9.7)	6.77	526 (11.4)	8.04
Hypotension (BIcMQ)	403 (8.6)	5.98	465 (10.0)	7.05
Without loop or high-ceiling diuretics	1333 (100.0)		1342 (100.0)	
Acute renal failure (SMQ)	104 (7.8)	4.88	101 (7.5)	4.70
Volume depletion (BIcMQ)	106 (8.0)	5.04	114 (8.5)	5.38
Hypotension (BIcMQ)	92 (6.9)	4.34	103 (7.7)	4.85
With loop or high-ceiling diuretics	3869 (100.0)		3864 (100.0)	
Acute renal failure (SMQ)	483 (12.5)	8.99	446 (11.5)	8.30
Volume depletion (BIcMQ)	377 (9.7)	6.99	452 (11.7)	8.46
Hypotension (BIcMQ)	338 (8.7)	6.22	396 (10.2)	7.35

Source data: [SCS appendix 2, c35146126, Tables 2.2.1.12 to 15, 2.2.8.11 to 14, 2.2.9.15 to 18]

Discontinuation due to adverse events

The frequencies of patients with AEs leading to discontinuation of study medication were similar between treatment groups. The most commonly reported (≥0.2% in at least one group) of these events are

summarised in Table 49. On the PT level, the most frequently reported AEs leading to discontinuation were cardiac failure and death.

Table 49. Patients with AEs leading to discontinuation of study medication in SAF-HF1 (frequency ≥0.2% in at least one treatment group at the PT level) – TS

MedDRA SOC MedDRA PT	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs
Number of patients	5202 (100.0)		5206 (100.0)	
Total with AEs leading to discontinuation	899 (17.3)	11.36	912 (17.5)	11.47
Cardiac disorders	261 (5.0)	3.28	224 (4.3)	2.80
Cardiac failure	135 (2.6)	1.70	110 (2.1)	1.38
Myocardial infarction	21 (0.4)	0.26	16 (0.3)	0.20
Acute myocardial infarction	17 (0.3)	0.21	19 (0.4)	0.24
Cardiac arrest	13 (0.2)	0.16	17 (0.3)	0.21
Cardiac failure congestive	16 (0.3)	0.20	11 (0.2)	0.14
Cardiac failure acute	14 (0.3)	0.18	8 (0.2)	0.10
Cardiogenic shock	8 (0.2)	0.10	6 (0.1)	0.07
Infections and infestations	109 (2.1)	1.37	136 (2.6)	1.70
Urinary tract infection	13 (0.2)	0.16	24 (0.5)	0.30
Pneumonia	23 (0.4)	0.29	19 (0.4)	0.24
COVID-19	18 (0.3)	0.23	12 (0.2)	0.15
COVID-19 pneumonia	5 (0.1)	0.06	12 (0.2)	0.15
Sepsis	8 (0.2)	0.10	9 (0.2)	0.11
Septic shock	7 (0.1)	0.09	8 (0.2)	0.10
General disorders and administration site conditions	118 (2.3)	1.48	123 (2.4)	1.54
Death[1]	57 (1.1)	0.72	69 (1.3)	0.86
Sudden cardiac death	19 (0.4)	0.24	12 (0.2)	0.15
Sudden death	11 (0.2)	0.14	14 (0.3)	0.17
Cardiac death	10 (0.2)	0.13	8 (0.2)	0.10
Renal and urinary disorders	90 (1.7)	1.13	83 (1.6)	1.04
Renal impairment	25 (0.5)	0.31	30 (0.6)	0.37
Acute kidney injury	19 (0.4)	0.24	16 (0.3)	0.20
Renal failure	17 (0.3)	0.21	8 (0.2)	0.10
Chronic kidney disease	16 (0.3)	0.20	15 (0.3)	0.19
Nervous system disorders	77 (1.5)	0.97	82 (1.6)	1.02
Ischaemic stroke	20 (0.4)	0.25	18 (0.3)	0.22
Dizziness	14 (0.3)	0.18	7 (0.1)	0.09
Cerebrovascular accident	12 (0.2)	0.15	13 (0.2)	0.16
Gastrointestinal disorders	47 (0.9)	0.59	50 (1.0)	0.63
Dyspepsia	9 (0.2)	0.11	2 (<0.1)	0.02
Vascular disorders	33 (0.6)	0.41	35 (0.7)	0.44
Hypotension	12 (0.2)	0.15	17 (0.3)	0.21

1 Deaths not attributed to another PT by the investigator. The frequencies of patients with fatal AEs were balanced between treatment groups.

Source data: [SCS appendix 2, c35146126, Table 2.1.1.6]

Post marketing experience

See the periodic benefit-risk evaluation report (PBRER) for post-marketing data in patients with T2DM.

On 17 Jun 2021, empagliflozin was approved in the EU for use in patients with HFrEF (with or without T2DM). There has been no substantial post-marketing experience in these patients.

2.5.1. Discussion on clinical safety

In SAF-HF1, 10408 patients were treated, and 28.2% of patients prematurely discontinued study medication (including patients who died). More than 70% of patients had an exposure for at least 52 weeks. The exposure is considered acceptable to perform a safety evaluation.

The number of AEs and severe AEs were similar for empagliflozin compared to placebo, but the number of cardiac events were lower for empagliflozin vs. placebo. A similar number of total AEs could therefore result from a larger number of other AEs. Based on the most frequently reported AEs, this number of events is also similar for empagliflozin compared to placebo, except for hypotension (empagliflozin 372 (7.1%) placebo 313 (6.0%)) and urinary tract infections (empagliflozin 314 (6.0%) placebo 259 (5.0%)). Hypotension is a known side-effect for SGLT2i treatment and can be related to other symptoms, such as syncope and fall, discussed below. Urinary tract infections and genital infections are also known side effects of SGLT2i treatment.

The safety analyses in SAF-HF1 were also performed focused on AESIs and specific AEs. The numbers of events with acute renal failure (empagliflozin 547 (10.5%), placebo 587 (11.3%)), keto-acidosis (broad BIcMQ: empagliflozin 63 (1.2%), placebo 77 (1.5%); narrow BIcMQ: empagliflozin 4 (0.1%), placebo 6 (0.1%)) and hepatic injury (empagliflozin 197 (3.8%), placebo 248 (4.8%)) were not larger for empagliflozin compared to placebo. The number of AEs leading to LLA was also similar between placebo and empagliflozin treatment (empagliflozin 29 (0.6%), placebo 33 (0.7%)), both for patients with and without diabetes. The numbers of bone fractures (empagliflozin 179 (3.4%), placebo 171 (3.3%)) and confirmed hypoglycaemic events (empagliflozin 101 (1.9%), placebo 108 (2.1%)) were also similar for empagliflozin vs. placebo, except for hypoglycaemic events in T1DM, but this consisted of a very small number of events and therefore not contributing to the evaluation (empagliflozin 2/5 (40%), placebo 1/5(20%)).

As expected from previous safety evaluation and reported ADRs, urinary tract infections (empagliflozin 402 (7.7%), placebo 335 (6.4%)) and genital infections (empagliflozin 101 (1.9%), placebo 35 (0.7%)) were more common in the empagliflozin group than in the placebo group. The number of complicated urinary tract infections, urosepsis or pyelonephritis, was also more in the empagliflozin group vs placebo. The treatment difference was most pronounced in female patients for urosepsis or pyelonephritis (empagliflozin 20/1895 (1.1%), placebo 6/1915 (0.3%)) and for patients without diabetes (empagliflozin 15/2633 (0.6%), placebo 8/2620 (0.3%)). It is known that female subjects are more susceptible for urinary tract infection, and this may partly explain the increased incidence in female subjects with empagliflozin treatment. Patients without diabetes normally do not have glucosuria, but this is altered by SGLT2i treatment and could therefore increase the risk of urinary tract infection. The number of complicated genital infections was similar between empagliflozin and placebo (empagliflozin 14 (0.3%), placebo 14 (0.3%)). Urinary tract infections, including urosepsis and pyelonephritis, and genital infections are included in Section 4.8 of the SmPC. The current observations are in line with the described ARD in the SmPC.

Volume depletion was also more frequent with empagliflozin treatment (empagliflozin 566 (10.9%), placebo 483 (9.3%)), including the number of symptomatic hypotension and syncope. Serious volume depletion events were also more frequent with empagliflozin treatment (empagliflozin 113 (2.2%), placebo 91 (1.7%)). During treatment with empagliflozin, the intensity of diuretic therapy or non-diuretic anti-hypertensive therapy was more frequently reduced. Volume depletion, including hypotension, is described in Section 4.4 and 4.8 of the SmPC. The current observations are in line with de described ARD in the SmPC.

In the EMPEROR Reduced trial, falls were reported for more patients in the empagliflozin vs the placebo group. In the current SAF-HF1, the treatment difference in the number of reported falls is less pronounced (empagliflozin 261 (5.0%), placebo 249 (4.8%)). In the EMPEROR preserved trial, the number of falls is similar for the empagliflozin group vs placebo (empagliflozin 213 (7.1%), placebo 219 (7.3%)), but falls were reported much more frequent in the EMPEROR preserved trial compared to the EMPEROR-reduced (empagliflozin 43 (2.3%), placebo 27 (1.4%)). This is probably due to a difference in the study population (e.g. difference in percentage of female subjects). The difference between treatments in reported falls in the SF-HF1 and EMPEROR-preserved is considered small. The number of falls was also more frequent in the Asian subgroup with empagliflozin vs placebo. This was present in both the EMPEROR-reduced (empagliflozin 6/337 (1.8%), placebo 1/334 (0.3%)) and EMPEROR-preserved trial (empagliflozin 39/413 (9.4%), placebo 26/411 (6.3%)). The Applicant describes that each event of fall in the Asian patients of EMPEROR-preserved trial was extensively medically reviewed for the origin of the fall and that this did not lead to plausible pathophysiological causes and was not related to empagliflozin's mode of action (hypotension, volume depletion, hypoglycaemia), but mainly due to accidental falls.

Constipation is consistently more frequently reported in the empagliflozin group compared to placebo group and is included in Section 4.8 of the SmPC.

In the SAF-HF1, the number of serious adverse events was not larger for empagliflozin compared to placebo (empagliflozin 2250 (43.1%), placebo 2502 (48.1%)).The reported number of myocardial infarctions and ischaemic stroke was slightly more for empagliflozin vs placebo (myocardial infarction: empagliflozin 53 (1.0%), placebo 44 (0.8%); ischaemic stroke: empagliflozin 61 (1.2%), placebo 55 (1.1%)). However, the differences between treatments are considered very small. This finding may be related to chance and this will not be pursued further.

The Applicant performed subgroup analyses to evaluate safety in special populations. As expected, the total number of AEs are reported more frequently in the older age groups, but similar for empagliflozin compared to placebo treatment. Volume depletion and genital infection are in general more frequent in the empagliflozin group, but the difference in frequency empagliflozin vs. placebo appears more pronounced in elderly patients (>75years). Elderly patients appear, therefore, more vulnerable for these side effects. The increased risk for volume depletion in elderly patients is described in Section 4.4 of the SmPC. For genital infections (Age 50-<65 empagliflozin 19 (1.6%), placebo 8 (0.7%); age 65-<75: empagliflozin 32 (1.7%), placebo 10 (0.5%); age 75-<85 empagliflozin 43 (2.6%), placebo 11 (0.7%)), the increased risk in elderly is considered only mildly elevated and is not deemed necessary to be included in section 4.8.

As expected, the number of AEs is more in the lower eGFR subgroups compared to the higher eGFR subgroups, as the low eGFR subgroups represent a more vulnerable patient population. The effect of empagliflozin treatment on volume depletion appears larger in the eGFR subgroup 45-<60 compared to the higher eGFR subgroups (eGFR 60 - <90: empagliflozin 185 (8.6%), placebo 175 (8.2%); eGFR 45-<60: empagliflozin 182 (13.8%), placebo 121 (9.1%)). However, in the eGFR subgroup 30 -<45 (empagliflozin 117 (12.0%), placebo 122 (12.4%)), there was no difference in volume depletion frequency between empagliflozin and placebo and the observation for the eGFR subgroup 45 -<60 is therefore not consistently observed.

There was no difference in the number or the type of AEs leading to discontinuation between the empagliflozin group and the placebo group.

2.5.2. Conclusions on clinical safety

The safety profile of empagliflozin in patients with HF, with or without diabetes, appears in general similar to the safety profile in patients with HFrEF and/or T2DM. No new large safety issues have been identified.

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/was requested to submit an updated RMP version with this application (RMP v16, date of final sign off: 04 Aug 2021). The main proposed RMP changes were the following:

***Part I. Product overview**

This part is proposed to be updated in order to include information on the proposed extension of indication to add the treatment of patients with Heart Failure with preserved ejection fraction.

***Part II. Safety specification**.

The following modules have been updated:

MODULE SI Epidemiology of the indications and target populations

The MAH has updated all data of epidemiology concerning the new proposed indication.

MODULE SIII clinical trial exposure

The MAH has updated this section including data from clinical trials in patients with HFpEF (trials 1245.110, 1245.148 and 1245.167).

Four safety analysis sets were described as used for clinical trial exposure calculation:

SIII.Table 1 Overview of safety analysis sets

SAF	Description	Trials included
SAF-HF4	Randomised, placebo-controlled clinical trials in patients with HFpEF	1245.110, 1245.148(HFpEF arm),1245.167
SAF-HF5	Randomised, placebo-controlled clinical trials in patients with HFrEF	1245.121, 1245.168
SAF-43[2]	Randomised, double-blind, placebo-controlled trials in patients with T2DM	1245.4, 1245.9, 1245.10, 1245.15, 1245.19, 1245.20, 1245.23 (Met only and Met+SU), 1245.25, 1245.29, 1245.33, 1245.35, 1245.36, 1245.38, 1245.48, 1245.49, 1245.107, 1275.9, 1275.19, 1276.10
SAF-POOL2[2]	Randomised, placebo-controlled clinical trials across indications HFpEF, HFrEF and T2DM (comprisingSAF-H4, SAF-HF5 and SAF-43)	1245.4, 1245.9, 1245.10, 1245.15, 1245.19, 1245.20, 1245.23 (Met only, Met+SU), 1245.25, 1245.29, 1245.33, 1245.35, 1245.36, 1245.38, 1245.48, 1245.49, 1245.107, 1245.110, 1245.121, 1245.148, 1245.167, 1245.168, 1275.9, 1275.19, 1276.10

[1] Data from trial 1245.148 was not available at the time of database lock for the HFrEF submission; the trial is therefore not included in the pooling.

[2] The data of extension trial 1245.31 are contained in the core trials 1245.19, 1245.20, and 1245.23.

Data source: data on file, SAF-43 Table 31.3.1.1; SAF-HF5(HFrEF), Tables 1.1 and 1.2; and SAF-HF4(HFpEF), Tables 1.1 and 1.2

MODULE SIV Populations not studied in clinical trials

Exposure of special populations included or not in clinical trial development programs has been updated.

MODULE SV Post-authorisation experience

This module has been updated with the most recent data on post-authorisation exposure up to April 2021.

MODULE SVII Identified and potential risk

No new safety concerns have been identified by the MAA following new data from clinical trials in patients with HFpEF.

The MAH has updated the characterisation of the identified and potential risks, with risk analyses from HFpEF trials (1245.110, 1245.148-HFpEFarm and 1245.168).

***Part VI Summary of the risk management plan**

This part has been updated to include information on the proposed indication.

No new safety concern has been identified.

Regarding the pharmacovigilance plan, no new additional pharmacovigilance activities have been proposed, which is endorsed.

No new additional risk minimisation measures have been added either, which is also considered acceptable.

Overall, the changes of the RMP are acceptable.

2.6.1. Overall conclusion on the RMP

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

The PRAC considered that the risk management plan version 16.0, date of final sign off: 04 Aug 2021, is acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to Infiltrative disease or Takotsubo cardiomyopathy has been added to the product information. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic heart failure is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues, or the heart can only provide adequate blood supply at the expense of elevated left ventricular filling pressure. Symptoms include dyspnoea (shortness of breath), oedema (build-up of fluid in the body tissues), persistent coughing and wheezing (due to build-up of fluid in the lungs), tiredness or fatigue, reduced appetite or nausea, confusion, disorientation, and increased heart rate.

Worldwide, heart failure has a prevalence of 1% to 2% and affects over 64 million people as of 2017. In the US alone the prevalence is 6.2 million, and this number has been projected to grow to over 8 million by 2030. HF is associated with premature mortality and frequent hospitalisations. HF contributes to 1 in 9 deaths, and the estimated 5-year survival is about 50% at the time of diagnosis. HF is the leading cause of hospitalisation in patients above 65 years of age.

Patients with HF are categorised according to measurements of left ventricular ejection fraction (LVEF); patients with LVEF ≤40% are considered to have HFrEF, and those with LVEF >50% are considered to have HFpEF. LVEF of >40% to <50% is considered as HFpEF in many clinical trials and registries, although more recently, the term HF with "mid-range" EF (HFmEF) was introduced to categorise this group separately. The relative prevalence of HFpEF among HF patients is approximately 50% and appears to be increasing. HFrEF and HFpEF differ in several aspects, including underlying aetiologies, demographics, co-morbidities, and responses to treatment. Patients with HFpEF tend to be older, more often women, and more likely to have a history of hypertension and atrial fibrillation than patients with HFrEF. Although HFpEF and HFrEF have similarly profound impacts on patient quality of life and prognosis, historically, therapies shown to improve prognosis in patients with HFrEF do not seem to be effective in patients with HFpEF.

3.1.2. Available therapies and unmet medical need

HFrEF can be treated with drugs that act to attenuate the overactivation of endogenous neurohormonal systems. The therapeutic options for patients with HFpEF are limited.

Recommendations for the treatment of HFrEF include the use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA), and the use of implantable devices like ICD and CRT, all of which have been shown to reduce mortality in patients with HFrEF.

For patients with HFpEF, no therapy has been proven to be superior to control based on the pre-specified primary endpoint in any prior pivotal clinical outcome study in patients with HFpEF. According to the current guidelines, the management of HFpEF involves control of congestive symptoms, usually with diuretics, and the treatment of co-morbidities. A lack of therapeutic options that can reduce the risk of mortality and hospitalisation in these patients represents an unmet medical need.

Empagliflozin

Empagliflozin (Jardiance) is an orally administered, potent and selective inhibitor of the human sodium-glucose cotransporter-2 (SGLT 2) developed by Boehringer Ingelheim (BI). By inhibition of SGLT 2 in the

kidneys, empagliflozin reduces the reabsorption of glucose by the kidneys leading to increased urinary glucose excretion and, in consequence, to a lowering of blood glucose. Empagliflozin is approved for the treatment of T2DM worldwide as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes. In the United States and several other countries, it is also approved to reduce the risk of CV death in patients with T2DM and established CV disease. On 17 Jun 2021 empagliflozin was approved in the EU for the treatment of heart failure with reduced ejection fraction based on the EMPEROR-Reduced study (1245.121) results.

Empagliflozin exerts its effect by preventing sodium and glucose reabsorption. While natriuresis will be compensated within days of drug administration through changes in tubulo-glomerular feedback, glucosuria will last for as long as the medication is used. This leads to long-lasting hemodynamic changes associated with modest osmotic diuresis, blood pressure-lowering effect, improvement in arterial stiffness, reduction in oxidative stress, and decrease in rate pressure product, an indirect measure of myocardial oxygen demands, with no increase in HR and no effect on sympathetic nerve activity. The non-glycosuric physiological and hemodynamic adaptations under empagliflozin may, therefore, provide benefits for patients with HF with or without diabetes.

3.1.3. Main clinical studies

Based on the results of trial 1245.25 (EMPA-REG OUTCOME) in patients with T2DM and established CV disease, BI initiated a phase III program for empagliflozin 10 mg once daily in chronic heart failure regardless of diabetes status, including two pivotal CV outcome trials ("EMPEROR") in patients with HFrEF and HFpEF.

Based on the results of the pivotal trial 1245.110, BI sought an extension of indication, i.e. for the treatment of symptomatic chronic heart failure.

EMPEROR-preserved – trial 1245.110

Trial 1245.110 was carried out at 622 clinical sites in 23 countries in Europe, Latin America, North America, Asia, and others (South Africa, Australia, India). In total, 5988 patients were randomised to double-blind empagliflozin 10 mg (2997 patients) or placebo (2991 patients) once-daily treatment. Randomisation was stratified by region, diabetes history, LVEF, and eGFR $(CKD\text{-}EPI)_{cr}$ at screening. Patients were to be treated with randomised study medication in addition to standard of care (in accordance with local/international guidelines) until the required number of patients with adjudicated primary endpoint events was expected to be reached. The median exposure to study medication was about 23 months. After the last intake of study medication, patients were to be followed up for 30 days.

The aim of the EMPEROR-preserved trial is to investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HFpEF. The primary endpoint was the time to the first event of adjudicated CV death or adjudicated HHF. The two key secondary endpoints (confirmatory) were; the occurrence of adjudicated HHF (first and recurrent) and eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline.

Patients in this trial represented a population with chronic heart failure with preserved ejection fraction (LVEF: 33.1% of patients had <50%, 34.4% had 50 to <60%, and 32.5% had ≥60%; mean 54.3%, SD 8.8) with a NYHA class of II (81.5%), III (18.1%), or IV (0.3%, 18 patients). The average age was 71.9 years (SD 9.4); 44.7% were women, 75.9% White, 13.8% Asian, and 4.3% Black/African American. About half of patients (48.9%) had T2DM; 10 patients (0.2%) had T1DM. Half of the patients (49.9%) had an eGFR of <60 mL/min/1.73 m2 (of whom 309 patients, 5.2%, had an eGFR of <30) at baseline. At study baseline, patients were treated with drugs for symptoms and co-morbidities; 80.7% of patients were

treated with ACE inhibitors/ARBs/ARNi, 86.3% with beta-blockers, 86.2% with diuretics (37.5% MRAs) and 70.8% with lipid-lowering drugs. Demographics and baseline characteristics were balanced between the treatment groups.

3.2. Favourable effects

Cardiovascular endpoints

CV death or HHF (primary endpoint) occurred in a lower proportion of patients in the empagliflozin group than in the placebo group (empagliflozin 415/2997, 13.8%; placebo 511/2991, 17.1%), and the risk of CV death or HHF was reduced with empagliflozin treatment compared with placebo (HR empagliflozin vs placebo 0.79, 95% CI 0.69 to 0.90). Adjudicated HHF (first or recurrent, key secondary endpoint) occurred in fewer patients in the empagliflozin group than in the placebo group (HR 0.73, 95% CI 0.61 to 0.88). Fewer patients were reported with CV death with empagliflozin versus placebo, but this difference was not statistically significant (HR 0.91, 95% CI 0.76 to 1.09).

Renal endpoints

An initial dip in eGFR was observed with empagliflozin treatment, followed by a slower decrease in eGFR over time. The change of eGFR slope from baseline (key secondary endpoint) showed a slower decline in eGFR in the empagliflozin group, with an estimated difference in slope of 1.363 mL/min/1.73 m^2 per year vs placebo (99.9% CI 0.861 to 1.865). The results for the composite renal endpoint (i.e. chronic dialysis, renal transplant, or sustained reduction in eGFR; secondary/exploratory endpoint) are similar for empagliflozin vs. placebo (empagliflozin 108/2997 (3.6%), placebo 112/2991 (3.7%), HR 0.95 95% CI 0.73 to 1.24). The proportion of patients progressing to macroalbuminuria (secondary/exploratory endpoint) was less with empagliflozin vs. placebo (HR 0.82, 95% CI 0.68, to 0.98).

Mortality

All-cause mortality was similar in both treatment groups (HR 1.00, 95% CI 0.87 to 1.15). The number of CV death are described above. The number of non-CV death was larger with empagliflozin, but this difference was not statistically significant (empagliflozin 203/2997, placebo 183/2991, HR 1.13, 95% CI 0.92 to 1.38).

Patient reported outcomes

The change from baseline in KCCQ clinical summary score was a secondary/exploratory endpoint. The mean treatment difference in change was 1.32, 95% CI 0.45 to 2.19. The proportion of patients achieving a clinically relevant change (i.e. 5 points) was larger in the empagliflozin group compared to placebo (empagliflozin 1126 patients, 41.7%; placebo 1034 patients, 38.7%).

Elderly patients

In elderly patients, i.e. age ≥ 70 years, the point estimate of treatment effect was larger compared to patients < 70 for the primary endpoint (age ≥70 years HR 0.75, 95% CI 0.64-0.95, age <70 years HR 0.88, 95% CI 0.70-1.11) and key secondary endpoint (HHF) (age ≥70 years HR 0.65, 95% CI 0.52-0.82, age <70 years HR 0.92, 95%CI 0.67-1.26).

In addition, the applicant discussed efficacy results and the safety data of both EMPEROR trials in patients aged ≥85 years. The number of patients aged ≥85 years that were included is 483 patients. The data do not suggest that patients aged ≥85 years benefit less form treatment of the indication of chronic symptomatic heart failure. The efficacy in general appears similar. The safety profile also appears similar across the age groups. The applicant therefore concluded that "limited therapeutic experience" in the elderly population is no longer suitable and amended sections 4.2 and 4.4 in the SmPC and the Package Leaflet to remove the warning. The amendments proposed by the MAH are considered acceptable.

3.3. Uncertainties and limitations about favourable effects

Effects independent of LVEF

Although HFpEF has been defined from a LVEF >40%, the range between 40 and 50% is currently considered HFmEF, and this group of patients may differ in the aetiology and treatment response compared to patients with LVEF >50%/HFpEF. Retrospective analyses have suggested that the benefits of neurohormonal antagonists in patients with HFrEF extend to those with a mildly reduced ejection fraction (Dewan P et al. Eur J Heart Fail 2020). This may affect the interpretation of the overall efficacy results. Stratified randomisation was performed for LVEF subgroups (i.e. LVEF <50%, LVEF 50-<60% and LVEF ≥60%), and the number of patients was equally distributed between the LVEF subgroups. Subgroup analyses for LVEF were performed for the primary and key secondary endpoints. Although the p value for interaction was not significant (p=0.2098) for the primary endpoint (CV death or HHF), the effect was more pronounced in patients with LVEF <50% compared to ≥60%, but was still significant for the group LVEF 50-<60% and remained positive for LVEF≥60% (LVEF <50% HR 0.71, 95%CI 0.57-0.88; LVEF 50-<60%, HR 0.80, 95%CI 0.64-0.99; LVEF >60%, HR 0.87, 95%CI 0.69-1.10). As the effect of empagliflozin on the primary endpoint was beneficial for all LVEF subgroups, the indication for the treatment of heart failure in patients with HFpEF is acceptable. As the indication for the treatment of heart failure is for all types of heart failure, the wording *"for the treatment of symptomatic chronic heart failure."* is considered acceptable.

It could, however, be suggested that there is a modification of the treatment effect in subjects with higher LVEF for the key secondary endpoint, i.e. adjudicated HHF (first and recurrent), where the point estimate for the subgroup LVEF ≥60% is HR 1.06 (95%CI 0.76-1.46) and p for interaction 0.0077. This could indicate that patients with LVEF ≥60% benefit less from treatment with empagliflozin. The lower HR in the subgroup ≥70%, however, contradicts this suggestion, although the number of subjects was small in this subgroup. The analyses on the contribution of HHF events by number of events experienced per patient showed that only a small number of patients contributed to the high number of recurrent HHF in the empagliflozin group, which may contribute to the imbalance in the analysis of the first and recurrent HHF in this subgroup. This may be related to chance.

Renal endpoints

The change of eGFR (CKD-EPI)cr slope from baseline was a key secondary endpoint and showed a slower decline in eGFR in the empagliflozin group, with an estimated difference in slope of 1.363 mL/min/1.73 m2 per year. This endpoint has the limitation that a long treatment period, i.e. more than 2 years, is considered needed to confirm a beneficial effect. The effect on the renal composite endpoint is preferred for evaluation of renal effects. The effect of empagliflozin on the eGFR slope is not supported or confirmed by the observed effects on the composite renal endpoint (i.e. chronic dialysis, renal transplant, or sustained reduction in eGFR), as the results are similar for empagliflozin vs. placebo (empagliflozin 108/2997 (3.6%), placebo 112/2991 (3.7%), HR 0.95 95%CI 0.73, 1.24). However, the finding in the eGFR slope was supported by other additional pre-specified analyses, i.e. eGFR change from pre-treatment (baseline) to post-treatment

(follow-up; FU) analysed with ANCOVA, "true slope" (annualised change from pre-treatment to post-treatment weighted by time of FU squared) and progression to or reversal from macro-albuminuria. Although all exploratory, these findings indicate a consistent finding and this appears clinical relevant.

Mortality

All-cause mortality was similar in both treatment groups (HR 1.00, 95%CI 0.87 – 1.15). The number of non-CV death was larger with empagliflozin, but this difference was not statistically significant (empagliflozin 203/2997, placebo 183/2991, HR 1.13, 95%CI 0.92 – 1.38). The Applicant provided an extensive evaluation of the causes of non-CV death and could not show a specific increase in a cause of death during empagliflozin treatment. A beneficial effect on all-cause mortality with empagliflozin treatment in patients with HFpEF could not be demonstrated.

Patient reported outcomes

A larger difference in change from baseline in KCCQ clinical summary was observed in the empagliflozin vs. placebo group. Although statistically significant, the treatment difference appears modest, and the clinical relevance is questionable. The proportion of patients achieving a clinically relevant change (i.e. 5 points) was not defined as a secondary endpoint and resulted in a larger proportion of patients with clinically relevant change, but the difference in percentages is small. The treatment effects are considered small.

Combined treatment

Although effectiveness of treatment with ACEi/ARB, MRA's and/or ARNI's have not been demonstrated in patients with HFpEF, the majority of the patients used these treatments during the trial, i.e. ACEi/ARB's, 82.6%, MRA's 46.0%, ARNI's 4.4%. Empagliflozin was, therefore, evaluated on top of these medication, but these medications are not registered for the treatment of HFpEF. The Applicant described the baseline use of these agents in the trial population in Section 5.1 of the SmPC. The subgroup analysis for baseline use of ACEi/ARB/ARNI's and/or MRA's resulted in a similar risk reduction with empagliflozin vs. placebo for the primary and key secondary endpoints for patients using these agents compared to patients not using these agents at baseline. As the efficacy of empagliflozin appears consistent with vs without the use of these agents, it is considered acceptable that the indication for the treatment of HFpEF is independent of the baseline use of these agents.

3.4. Unfavourable effects

In SAF-HF1, 10408 patients were treated and 28.2% of patients prematurely discontinued study medication (including patients who died). More than 70% of patients had an exposure for at least 52 weeks. The exposure is considered acceptable to perform a safety evaluation.

Adverse events

The number of AEs and severe AEs were similar for empagliflozin compared to placebo (any AE; empagliflozin 81.4%, placebo 80.0%, severe AE; empagliflozin 26.5%, placebo 24.3%). Based on the most frequently reported AEs, this number of events is also similar for empagliflozin compared to placebo, except for hypotension (empagliflozin 372 (7.1%) placebo 313 (6.0%)) and urinary tract infections (empagliflozin 314 (6.0%) placebo 259 (5.0%)).

Deaths, serious adverse events and adverse events leading to treatment discontinuation

In the SAF-HF1, the number of serious adverse events was not larger for empagliflozin compared to placebo (empagliflozin 43.1%, placebo 48.1%). The frequencies of patients with AEs leading to discontinuation of study medication were similar between treatment groups (empagliflozin 17.5%, placebo 17.3%). There was not a difference between the type of AEs leading to discontinuation between the empagliflozin group and the placebo group. Number of deaths/mortality did not differ between the treatment groups.

Adverse events of special interest

Urinary tract infections

Urinary tract infections (empagliflozin 402 patients (7.7%), placebo 335 patients (6.4%)) were more common in the empagliflozin group than in the placebo group. The number of complicated urinary tract infections, urosepsis or pyelonephritis, was also more in the empagliflozin group vs placebo. The treatment difference was most pronounced in female patients for urosepsis or pyelonephritis (empagliflozin 20/1895 (1.1%), placebo 6/1915 (0.3%)) and for patients without diabetes (empagliflozin 15 patients (0.6%), placebo 8 patients (0.3%)).

Genital infections

Genital infections (empagliflozin 101 patients (1.9%), placebo 35 patients (0.7%)) were more common in the empagliflozin group than in the placebo group. The number of complicated genital infections was similar between empagliflozin and placebo (empagliflozin 14 patients (0.3%), placebo 14 patients (0.3%)). Genital infections with empagliflozin treatment were reported slightly more frequently in elderly patients (Age 50-<65 empagliflozin 19 (1.6%), placebo 8 (0.7%); age 65-<75: empagliflozin 32 (1.7%), placebo 10 (0.5%); age 75-<85 empagliflozin 43 (2.6%), placebo 11 (0.7%)).

Volume depletion

Volume depletion was also more frequent with empagliflozin treatment (empagliflozin 566 patients (10.9%), placebo 483 patients (9.3%)), including the number of symptomatic hypotension and syncope. Serious volume depletion events were also more frequent with empagliflozin treatment (empagliflozin 113 patients (2.2%), placebo 91 patients (1.7%)). During treatment with empagliflozin, the intensity of diuretic therapy or non-diuretic anti-hypertensive therapy was more frequently reduced.

Keto-acidosis

Based on the broad BIcMQ, events suggestive of ketoacidosis were reported for 63 patients (1.2%) in the empagliflozin group and for 77 patients (1.5%) in the placebo group. The narrow BIcMQ ketoacidosis included 4 patients (0.1%) in the empagliflozin group and 6 patients (0.1%) in the placebo group.

Lower limb amputation

The number of AEs leading to LLA was similar between placebo and empagliflozin treatment (empagliflozin 29 (0.6%), placebo 33 (0.7%)), both for patients with and without diabetes.

Decreased renal function

The numbers of events with acute renal failure (empagliflozin 547 patients (10.5%), placebo 587 patients (11.3%)) were not larger in the empagliflozin group compared to placebo.

Hepatic injury

The frequency of patients with hepatic injury was not higher in the empagliflozin group (197 patients (3.8%)) than in the placebo group (248 patients (4.8%)). The most frequent PTs were liver injury, hepatic function abnormal, and hepatic steatosis.

Hypoglycaemia

The numbers of confirmed hypoglycaemic events (empagliflozin 101 patients (1.9%), placebo 108 patients (2.1%)) were similar for empagliflozin vs. placebo, except for hypoglycaemic events in T1DM (empagliflozin 2/5 (40%), placebo 1/5(20%)).

Constipation

Constipation was reported for more patients in the empagliflozin group (153 patients (2.9%)) than in the placebo group (107 patients (2.1%)). The number of serious events or events leading to treatment discontinuation was low in both treatment groups.

Laboratory findings

In trials 1245.110 and 1245.121, haemoglobin and haematocrit values increased on treatment and then partially returned to baseline after treatment discontinuation in the empagliflozin group, with small decreases observed in the placebo group. There was a decrease in uric acid (urate) values in the empagliflozin group compared with the placebo group. After treatment discontinuation, uric acid values returned towards baseline in the empagliflozin group.

Vital signs

No meaningful changes in blood pressure (systolic or diastolic) or in heart/pulse rate were observed with empagliflozin treatment compared with placebo in any of the HF trials. There were no relevant differences in new ECG findings after baseline between empagliflozin and placebo.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of empagliflozin in patients with HF, with or without diabetes, appears in general similar to the safety profile in patients with T2DM. However, uncertainties remain about several unfavourable effects:

Urinary tract infection

Urinary tract infections were more common in the empagliflozin group than in the placebo group and the difference was most pronounced in female patients for urosepsis or pyelonephritis. It is known that female subjects are more susceptible for urinary tract infection, and this may partly explain the increased incidence in female subjects with empagliflozin treatment. Urinary tract infections, including urosepsis and

pyelonephritis, are included in Section 4.8 of the SmPC. The current observations are in line with the described ADRs in the SmPC.

Hypoglycaemia

The numbers of confirmed hypoglycaemic events were similar for empagliflozin vs. placebo, except for hypoglycaemic events in T1DM. But the latter consisted of a very small number of events (empagliflozin 2/5 (40%), placebo 1/5(20%)) and does therefore not contribute to the evaluation for increased risk.

Elderly patients

As expected, the total AEs are reported more frequently in the older age groups, but similar for empagliflozin compared to placebo treatment. Volume depletion and genital infection are in general more frequent in the empagliflozin group, but the difference in frequency vs. placebo appears more pronounced in elderly patients (>75years). Elderly patients appear, therefore, more vulnerable for these side effects. The increased risk for volume depletion in elderly patients is described in Section 4.4 of the SmPC. The increased risk for genital infections is not described in the SmPC, but this risk is considered only mildly elevated in elderly patients and is not deemed necessary to be included in section 4.8.

3.6. Effects Table

Table 50. Effects Table for Jardiance for the treatment of HFpEF

Effect	Short description	Unit	Empagliflozin (10mg)	Control (placebo)	Uncertainties (Unc) / Strength of evidence (SoE)	Trial
Favourable Effects						
CV death or HHF	Composite primary endpoint	N (%)	415/2997 (13.8)	511/2991 (17.1)	**SoE**: HR 0.79, 95%CI 0.69 to 0.90, p<0.0001 **Unc:** seems mainly driven by HHF	EMPEROR-preserved, (trial 1245.110)
First and recurrent HHF	adjudicated HHF event (key secondary endpoint)	N (%)	259 (8.6%)	352 (11.8%)	**SoE:** HR 0.79, 95%CI 0.69 to 0.90, p=0.0009 **Unc:** beneficial effect not demonstrated in all subgroups LVEF <50%: HR 0.57, 95%CI 0.42-0.79 LVEF 50-<60% : HR 0.66, 95%CI 0.48-0.91) LVEF ≥60%: HR 1.06, 95%CI 0.76-1.46	EMPEROR-preserved
Mortality	all-cause mortality	N (%)	422 (14.1%)	427/2991 (14.3%)	**SoE:** HR 1.00, 95%CI 0.87 to 1.15 **Unc:** CV death similar for empagliflozin and placebo (HR 0.91, 95%CI 0.76 to 1.09) number of non-CV death higher for empagliflozin	EMPEROR-preserved
eGFR slope	eGFR slope of change from baseline (key secondary endpoint)	Slope [/year] estimate (95% CI)	−1.253 (−1.465, −1.041)	−2.616 (−2.827, −2.405)	**SoE:** Difference vs placebo: 1.363, 99%CI 0.861 to 1.865, p<0.0001 **Unc:** not supported by combined renal endpoint	EMPEROR-preserved
Unfavourable Effects						
AEs		%	80.0	81.4		SAF-HF1, (trial 1245.110 and 1245.121)

Effect	Short description	Unit	Empagliflozin (10mg)	Control (placebo)	Uncertainties (Unc) / Strength of evidence (SoE)	Trial
SAEs		%	43.2	48.1	Mainly driven by cardiac events	SAF-HF1
Volume depletion	(including hypotension)	N (%)	566 (10.9)	483 (9.3)	Serious volume depletion events more frequent with empagliflozin. Volume more frequent in elderly patients	SAF-HF1
Genital infections		N (%)	101 (1.9)	35 (0.7)	Seemingly effect of treatment more outspoken for elderly patients	SAF-HF1
Urinary tract infections		N (%)	402 (7.7)	335 (6.4)	Difference was most pronounced in female patients for urosepsis or pyelonephritis	SAF-HF1

Abbreviations: AE, adverse events; CI, confidence interval; CV, cardio vascular; GFR, glomerular filtration rate; HR, hazard ratio; N, number; SAE, serious adverse events
Notes: Favourable effect based on EMPEROR preserved (Trial 1245.110), unfavourable effects based on SAF-HF1

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

HF is a progressive syndrome with a high global prevalence. A treatment-induced decrease in HF-related complications such as HHF and CV death is therefore important. Especially for patients with HFpEF, the registered treatment options are limited. The finding in the EMPEROR-preserved trial of decreased occurrence of HHF or CV death with empagliflozin treatment (HR 0.79, 95%CI 0.69 to 0.90) is considered an important benefit. During the trial period, the number of patients who would need to have been treated with empagliflozin to prevent one primary event (NNT) was 31 (95%CI 20 to 69). Although this effect seems mainly due to the decrease in HHF and to a lesser extent to the decrease in CV death, it is still regarded as clinically relevant, especially as the normal progression of HF is still associated with a high frequency of rehospitalizations. Importantly, there was, however, no benefit on all-cause mortality. The number of non-CV death was larger with empagliflozin, but this difference was not statistically significant. The Applicant provided an extensive evaluation of the causes of non-CV death and could not show a specific increase in a cause of death during empagliflozin treatment.

This current application is an indication for the treatment of chronic heart failure independent of LVEF. For the primary endpoint a positive effect of empagliflozin treatment was observed overall and in all the pre-defined LVEF subgroups. The p for interaction was not significant. However, for the secondary endpoint (first and recurrent HHF) the HR point estimate and the level of precision for the subgroup LVEF ≥60% is 1.06 (95%CI 0.76-1.46, p for interaction p=0.0077). This finding in subjects with LVEF ≥60% could indicate a decrease in efficacy in the higher LVEF subgroups for this endpoint. The lower HR in the subgroup ≥70%, however, contradicts this suggestions, although the number of subjects was small in this subgroup. The analyses on the contribution of HHF events by number of events experienced per patient showed that only a small number of patients contributed to the high number of recurrent HHF in the empagliflozin group, which may contribute to the imbalance in the analysis of the first and recurrent HHF in this subgroup. This may be related to chance. Based on these findings it is not considered supported that there is a decrease in efficacy in patients with higher LVEF.

The finding of a slower eGFR slope decline with empagliflozin treatment (estimated difference in slope of 1.733 mL/min/1.73 m2 per year vs placebo (99.9% CI 0.669, 2.796; p<0.0001)), could be regarded as not convincing. Although this endpoint was a key secondary endpoint, the slope analysis modelling is better suited in providing descriptive information on renal outcomes than providing definitive statistical and clinical evidence of a renal effect as it is used now. The data on the eGFR slope were not supported by a beneficial effect on the preferred renal composite (secondary/exploratory) outcome endpoint (i.e. chronic dialysis,

renal transplant, or sustained reduction in eGFR) (HR 0.95 95%CI 0.73 to 1.24). The results are also not fully in line with earlier observations in patients with HFrEF or T2DM. However, the finding in the eGFR slope was supported by other additional pre-specified analyses, i.e. eGFR change from pre-treatment (baseline) to post-treatment (follow-up; FU) analysed with ANCOVA, "true slope" (annualised change from pre-treatment to post-treatment weighted by time of FU squared) and progression to or reversal from macro-albuminuria. Although all exploratory, these findings indicate a consistent finding and this appears clinical relevant.

In the EMPEROR-preserved trial, the KCCQ 'clinical summary score' was used to measure as a secondary/exploratory endpoint of a patient-reported outcome. Although statistically significant, the treatment difference appears modest, and the clinical relevance is questionable. The Applicant also provided the proportion of patients achieving a clinically relevant change (i.e. 5 points), but again the difference in percentages is small. The potential beneficial effects of empagliflozin on HF-related symptoms are not established robustly and are, therefore, of questionable importance.

Treatment with empagliflozin in patients with HFpEF generally revealed no new large safety findings compared with the known safety profile of empagliflozin in patients with HFrEF and/or T2DM. The numbers of reported AEs and SAEs were equally distributed between the treatment groups. As expected, genital infections, urinary tract infections and volume depletion were more reported during empagliflozin treatment, but these are known side-effects and included in the SmPC. They have previously not affected the benefit-risk balance to a negative ratio for the indication for the treatment of HFrEF and/or T2DM.

3.7.2. Balance of benefits and risks

The MAH agreed to amend the initially applied indication i.e.

The final agreed indication is:

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure ~~with reduced ejection fraction~~.

The reduced incidence of HHF or CV death is an important benefit and significantly contributes to a positive B/R ratio. It is important to point out that this finding is mainly driven by an effect on HHF, as no relevant reduction in CV death was observed.

A beneficial effect on the primary endpoint was observed across all LVEF subgroups and the indication for the treatment of heart failure in patients with HFpEF is acceptable. As the indication for the treatment of heart failure is for all types of heart failure, the wording "*for the treatment of symptomatic chronic heart failure."* is considered acceptable.

Results on the key secondary endpoint, i.e. first and recurrent HHF, could indicate that there a decrease in effect in patients with higher LVEF (≥60%). Additional analyses, i.e. further subgroup analyses based on LVEF and analyses on the contribution of HHF events by number of events experienced per patient, suggest that this finding is related to chance.

Treatment with empagliflozin in patients with HFpEF generally revealed no new large safety findings compared with the known safety profile of empagliflozin in patients with HFrEF and/or T2DM.

3.8. Conclusions

The overall B/R of Jardiance in the treatment of symptomatic chronic heart failure is positive.

4. Recommendations

Outcome

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

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

Extension of indication to add the treatment of treatment of symptomatic chronic heart failure based on the results from the clinical study 1245.110 EMPEROR-preserved.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and sections 1, 2 and 4 of the PIL are updated accordingly.
Further, the MAH applied for an additional year of market protection. The updated RMP v 16.0 has also been submitted.
In addition, the statement 'sodium free' was re-located from section 2 of the SmPC to section 4.4. to comply with EMA'S QRD guidance and minor linguistic changes to the national translations are included in this submission.

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.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).