NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

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Process note:

Following the second appraisal committee meeting on 12 April 2023, the company, Boehringer-Ingelheim, resubmitted under the cost comparison process as outlined in the interim methods and process guide for the proportionate approach to technology appraisals. In line with this, the final scope and stakeholder list for the appraisal was updated to include dapagliflozin as a possible comparator.

Access the **final scope and final stakeholder list** on the NICE website.

Contents:

The following documents are made available to stakeholders:

1. **Company submission** from Boehringer-Ingelheim:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Patient group, professional group, and NHS organisation submission** from:
   a. British Society for Heart Failure

3. **External Assessment Report** prepared by BMJ-TAG

4. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]

Document B

Company evidence submission

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ID3945_ Empagliflozin Cost comparison evidence submission_Document_B	1.0	No	13/07/2023

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Tables and figures

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List of abbreviations

Acronym	Definition
AC	All-cause
ACEI	Angiotensin-converting enzyme inhibitors
AE	Adverse events
AESI	Adverse events of special interest
AF	Atrial flutter
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
ARNI	Angiotensin receptor-neprilysin inhibitors
AST	Aspartate aminotransferase
BMI	Body mass index
BNF	British national formulary
CABG	Coronary artery bypass grafting
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical practice research datalink
CRD	Centre for Reviews and Dissemination
CRM	Cardio-renal-metabolic
CRS	Cardio-renal syndrome
CSR	Clinical study report
CT	Computerised tomography
CVD	Cardiovascular death
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
EF	Ejection fraction
EMA	European medicines agency
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
GP	General practitioner
HbA1c	Glycated haemoglobin
HES	Hospital Episode Statistics
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalisation due to heart failure
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life

ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
IQR	Interquartile range
IRR	Incidence rate ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire - clinical summary score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire- total symptom score
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire - overall summary score
LLA	Lower limb amputation
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MA	Marketing authorisation
MACE	Major adverse cardiovascular events
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MMRM	Mixed model repeated measure
MRA	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network-meta-analysis
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAS	Patient Access Scheme
PD	Pulmonary disease
PICOS	Population, intervention, comparator, and outcomes
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PSSRU	Personal Social Services Research Unit
QoL	Quality of life
RCT	Randomised controlled trial
RS	Randomised set
RWE	Real-world evidence
SAE	Serious adverse event
SBP	Systolic blood pressure
SCR	Screened set

SD	Standard deviation
SGLT	Sodium-glucose co-transporter
SGLT1	Sodium-glucose co-transporter- 1
SGLT2	Sodium-glucose co-transporter- 2
SGLT2i	Sodium-glucose co-transporter- 2 inhibitor
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SLR	Systematic literature review
SmPC	Summary of medicinal product characteristics
STA	Single technology appraisal
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TA	Technology appraisal
UACR	Urine albumin-to-creatinine ratio
UK	United Kingdom
ULN	Upper limit of normal

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Population

Empagliflozin is currently recommended for the treatment of National Health Service (NHS) England patients with heart failure with reduced ejection fraction (HFrEF), i.e., left ventricular ejection fraction (LVEF) ≤40% (National Institute for Health and Care Excellence [NICE] technology appraisal TA773) (1). In order to achieve a recommendation that covers the full spectrum of chronic heart failure (HF), which is consistent with the marketing authorisation extension for empagliflozin for chronic HF regardless of ejection fraction (EF) (2), the current company submission considers evidence that reflects the remaining patient population not included in TA773, chronic HF patients with LVEF >40% (1).

This company submission provides evidence for the remaining chronic HF patient population that is reflected by the pivotal EMPEROR-Preserved trial. Similar to the EMPEROR-Reduced trial appraised by NICE in TA773, the EMPEROR-Preserved trial evaluated the effects of empagliflozin on the morbidity and mortality of patients with established HF, with or without type 2 diabetes mellitus (T2DM) (3). The trials were similar in design as both were phase III international, multicentre, randomised, double-blind, parallel-group, placebo-controlled trials (3-5). The main distinction between the EMPEROR-Reduced and EMPEROR-Preserved trials are in the inclusion criteria, with the former having enrolled patients with a baseline LVEF ≤40% (population assessed in the NICE appraisal TA773) and the latter having patients with LVEF >40% (focus population of this submission) (4, 5).

The chronic symptomatic HF population (LVEF >40%) defined in this company submission corresponds to an extension to the marketing authorisation (MA) of empagliflozin as the UK's first licensed treatment for adults with symptomatic chronic heart failure regardless of EF that was issued by the Medicines and Healthcare

products Regulatory Agency (MHRA) in June 2022. The details of MA issued by MHRA and NICE recommendation status of empagliflozin are summarised in Table 1.

Table 1. MA and NICE recommendation status of empagliflozin

Indication	Date of MA received by MHRA	NICE recommended/ date of NICE recommendation
Treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise in adults: • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes	May 2014	Recommended / 25 May 2016 & 25 March 2015
Treatment of symptomatic chronic HF regardless of EF	14 Jun 2022	Recommended for HF with EF≤40% / 9 March 2022 (Final guidance by NICE on Empagliflozin for treating chronic HF with reduced ejection)

Abbreviations: HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; marketing authorisation; NICE, National Institute for Health and Care Excellence; T2DM, type 2 diabetes mellitus.
Reference: (1, 2, 6, 7)

Comparator

The company is proposing that the appraisal of empagliflozin be considered under the NICE single technology appraisal (STA): cost-comparison process. The NICE guide for the technology appraisal (TA) process states that a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published TA guidance for the same indication (1).

For empagliflozin the relevant comparator is dapagliflozin, as it is a same class technology recommended in published NICE guidance for the same indication as empagliflozin. The wording of the recommendation from NICE guidance is: “Dapagliflozin is recommended, within its MA, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults.” (8).

The company wishes to pursue the same positioning as the NICE recommendation for dapagliflozin, as a treatment option for all adults with chronic symptomatic HF,

regardless of EF (9). A positive recommendation would result in the inclusion of empagliflozin in the NICE clinical guideline, NG106, as a recommended treatment option for all adults with chronic symptomatic HF.

This submission is based on several analyses that were conducted to provide evidence showing similar efficacy of empagliflozin versus dapagliflozin. A summary of the evidence includes the following:

- Empagliflozin and dapagliflozin belong to the same drug class of sodium-glucose transport protein 2 (SGLT2) inhibitors. Through SGLT2 inhibition, they simultaneously reduce renal reabsorption of glucose and sodium in the proximal tubules of the kidney, leading to increased urinary excretion of glucose and moderate natriuresis.
- A feasibility assessment was conducted to explore the similarities and differences between the EMPEROR-Preserved and DELIVER trials for empagliflozin and dapagliflozin, respectively. The feasibility assessment aimed to establish whether an indirect treatment comparison (ITC) (i.e., a Bucher analysis, a network-meta-analysis [NMA], or a matching-adjusted indirect comparison [MAIC]) was possible in consideration of data availability and between-study heterogeneity in terms of study design as well as patient demographic and disease characteristics. Based on the assessment, the two trials can be considered broadly similar in terms of baseline characteristics of included patients and study design (i.e., inclusion and exclusion criteria, and trial endpoints) (4, 10).
- Given that only two trials were of interest for this ITC, an NMA was ruled out as a potential method for comparison between empagliflozin and dapagliflozin because a network of studies requires more than two trials.
- A MAIC was not considered appropriate given that there were no clinically meaningful differences between patients' baseline characteristics that would be expected to influence the results. Any differences that were identified would not be feasible for adjustment as they reflect slight study design modifications in the DELIVER trial which cannot be matched in the EMPEROR-Preserved trial (i.e., inclusion of previously diagnosed LVEF≤40% patients, inclusion of urgent

HF visits within the primary endpoint). Furthermore, a MAIC is likely to increase rather than reduce decision making uncertainty as the results will reflect a smaller effective sample size after matching the populations of the two trials.

- Hence, the Bucher method is considered the most appropriate methodological approach for an ITC. The results from Bucher analyses showed that there is no statistically significant difference between empagliflozin versus vs dapagliflozin, in terms of primary outcomes (i.e., composite outcome for cardiovascular (CV) mortality or hospitalisation due to heart failure [HHF]) or secondary outcomes, including CV mortality, all-cause (AC) mortality, and HHF. This is further supported by a recently published independent meta-analysis (11).
- Both empagliflozin and dapagliflozin are anticipated to result in similar improvements in patients' health-related quality of life (HRQoL), given their equal efficacy and comparable safety profile. This is further supported by the similar improvement in mean change from baseline for Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), as shown in the respective clinical trials (i.e., EMPEROR-Preserved and DELIVER trials) (4, 10).
- Both drugs are positioned in the same place in the treatment pathway for HF and require similar treatment management (i.e., type, dose and frequency of administration, monitoring type and frequency, and treatment for adverse events).
- The safety profiles of empagliflozin and dapagliflozin are similar, as indicated by previous trials and clinical experience since 2014 when the drugs first became available for the treatment of T2DM. In particular, the EMPA-REG OUTCOME trial, examining the effect of empagliflozin on patients with T2DM, and EMPRISE study, examining the effectiveness of empagliflozin in routine care patients across a broad spectrum of cardiovascular risk, reinforced the safety profile of empagliflozin. This is further supported by evidence demonstrating similar adverse event rates as reported in the EMPEROR-Preserved and DELIVER trials.
- In terms of treatment acquisition costs, the price of empagliflozin and dapagliflozin is the same according to the British national formulary (BNF), and neither are subject to a Patient Access Scheme (PAS). Following the

comparable clinical efficacy and safety profiles, the resource use and costs for the drugs is anticipated also to be the same (12).

- Given the above, empagliflozin offers an additional treatment option for patients with chronic HF and mildly reduced or preserved EF, in accordance with the NICE recommendation for dapagliflozin (TA902) (8).

The decision problem addressed by this submission is summarised in Table 2.

Table 2. The decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with symptomatic chronic heart failure with left ventricular ejection fraction of 40% or more	Same	Not applicable
Intervention	Empagliflozin in combination with standard care (including loop diuretics and symptomatic treatments for co-morbidities)	Same	Not applicable
Comparator(s)	• Established clinical management without empagliflozin, including but not limited to loop diuretics and symptomatic treatments for co-morbidities • Dapagliflozin	Dapagliflozin is the comparator considered because the objective of this submission is to achieve the same recommendation as this drug, based on the similar efficacy (see section B.3.9) and comparable costs (see section B.4) of empagliflozin and dapagliflozin	Not applicable
Outcomes	The outcome measures to be considered include: • symptoms of heart failure • HHF • AC hospitalisation • mortality • cardiovascular mortality • kidney function	Same	Not applicable

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• adverse effects of treatment • HRQoL		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account."	Same	Not applicable
Subgroups to be considered	Not included in the draft scope	No subgroups were considered separately in the economic analysis	Not applicable

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	Not included in the draft scope	Broad prescribing of SGLT2i in primary and secondary care could reduce the inequality in terms of access to HF care in the UK	The socio-economic inequalities in CV disease present a major and persistent UK public health challenge. The UK-based population studies demonstrate that socio-economic deprivation is a strong risk factor for the development of HF and adverse HF outcomes (13, 14). Individuals in the lowest socio-economic group are 1.61 times more likely to experience incident HF than the most affluent individuals and on average, at a 3.5 years younger age with a greater comorbidity burden at the time of HF symptom onset (13). Findings from Conrad et al. (2018) report socio-economic inequalities among all age bands and by sex in the most deprived region, which were twice as high in younger adults (IRR 2.56; 95% CI, 2.30-2.85 in the 45-54 years age group vs. 1.17; 95% CI, 1.13-1.22 in the >85 years age group) (13). Making empagliflozin available as an additional SGLT2 treatment option would offer patients an additional choice and also provide further reassurance as they would not have to rely on only one recommended treatment option.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Socio-economic status has an impact on access to secondary care in the UK, and subsequently access to HF treatments. Moscelli et al. (2018) reported a statistically significant difference in waiting times across socio-economic groups for patients who attend the same hospital: patients living in more income-deprived areas waited longer (35% difference, or 43 days) than patients who lived in areas of a lesser deprivation (15). In addition to waiting longer, coronary heart disease patients in a lower socio-economic class were admitted to hospital less often than those in a higher class (15). McCartney et al. (2013) reported on a prospective study of 7,049 men and 8,353 women in the west of Scotland who were followed up for 37 years; the likelihood of a hospital admission for CV disease was 21% higher for female patients in highest socio-economic class than patients in lowest class. Those patients in social class IV and V (partly skilled and unskilled occupations) also stayed 25% longer in hospital than social class I and II (professional, managerial and technical occupations) (736 vs. 589 bed day/1,000 person-years, respectively) (16). These studies indicate that if patients in lower socio-economic classes utilise secondary care less often, their opportunity to access HF medications would also be lower, if they are solely prescribed in secondary care.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			BI support the UK Government's and NICE's commitment to the reduction of health inequalities, reiterated in the recent NICE five-year strategy publication (17, 18). Principle 9 of NICE's Social Value Judgements states that due regard must be given to reducing inequalities. It states that equality should be considered in relation to the nine protected characteristics in the Equality Act 2010 (age, disability, gender reassignment, race, religion or belief, sex, sexual orientation, marriage and civil partnership, pregnancy and maternity) and socio-demographic factors (18). Further, the COVID-19 Marmot review aims to reduce the widened gap in health inequalities and build a fairer society post pandemic (19). Broad prescribing of SGLT2i across primary and secondary care can support the reduction in disparity in terms of access to HF care across socio-economic groups within the UK. This appraisal further supports this objective by providing a treatment option for those patients with an LVEF >40%.

Abbreviations: CV, cardiovascular; HF, heart failure; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SGLT2i, sodium-glucose co-transporter 2 inhibitors; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

- Empagliflozin is an orally bioavailable, SGLT2 inhibitor, which has cardioprotective effects and improves HF-related outcomes (20, 21).

Empagliflozin's mechanism of action, MA, indication, mode of administration and list price are summarised in Table 3. Appendix C includes the draft summary of medicinal product characteristics (SmPC) for empagliflozin.

Table 3. Technology being evaluated

UK approved name and brand name	Empagliflozin (JARDIANCE®)
Mechanism of action	Empagliflozin is an orally bioavailable, reversible, highly potent and selective inhibitor of SGLT2 (20). Through SGLT2 inhibition, empagliflozin simultaneously reduces renal reabsorption of glucose and sodium in the proximal tubules of the kidney and leads to increased urinary excretion of glucose and moderate natriuresis. The molecular bases of empagliflozin's cardioprotective and nephroprotective effects are unknown; however, accumulating evidence suggests several distinct mechanisms are involved, including: • osmotic diuresis and natriuresis resulting in lowering of arterial pressure and stiffness and improvement in ventricular loading • improved myocardial and renal metabolism via switch to ketone bodies as the energy source • prevention of adverse cardiac remodelling through inhibition of inflammation, fibrosis, and cardiomyocyte cell death • direct inhibition of the Na+/H+ exchanger in myocardium, leading to reduction or reversal of cardiac injury, fibrosis and systolic dysfunction • prevention of ischaemia/reperfusion injury through decrease in calmodulin kinase II activity (21, 22)
Marketing authorisation/CE mark status	Empagliflozin currently holds EMA MA and is recommended by NICE for the treatment of T2DM as a monotherapy (25 May 2016) or as a combination therapy with insulin or other antidiabetic drugs (25 March 2015) (2, 6, 7). For treatment of chronic HFrEF, empagliflozin received EMA MA on 30 July 2021 and the NICE recommendation was published on 09 March 2022 (1, 2). The EMA MA was granted on 3 March 2022, and the UK MHRA MA was granted in June 2022 for symptomatic chronic HF. The current SmPC is provided in Appendix C (23).

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indication relevant to this submission***: Empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure. ***Other indications:*** • Empagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise o as monotherapy when metformin is considered inappropriate due to intolerance o in addition to other medicinal products for the treatment of diabetes.
Method of administration and dosage	10 mg oral empagliflozin once daily
Additional tests or investigations	None
List price and average cost of a course of treatment	List price of a pack of 28 tablets (10 mg) is £36.59. This equates to a cost of £1.31 per tablet per day for each patient.
Patient access scheme/commercial arrangement (if applicable)	None

Abbreviations: CHMP, Committee for Medicinal Products for Human use; EMA, European Medicines Agency; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus; UK, United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the disease for which the technology is indicated

B.1.3.1.1 Disease overview

- HF is a complex clinical syndrome caused by structural and/or functional abnormalities of the myocardium resulting in the impairment of ventricular filling and ejection of blood (24, 25).
- HF presents as either acute or chronic HF. Patients who are acutely decompensated might actually have chronic HF (24).
- There are limitations to the New York Heart Association (NYHA) classification as it is dependent on clinician's interpretation and poor agreement has been identified between cardiologists (24, 26).

- The recent European Society of Cardiology (ESC) guideline (2021) classifies HF based on LVEF; however, there are inconsistencies regarding the definition of different classes of HF observed in clinical trials and among clinical experts (24, 27).
- This company submission provides evidence for all patients with chronic HF and LVEF >40%, with the overall preferred outcome to have a broad recommendation for empagliflozin for all chronic HF patients in the NICE guideline NG106.

Clinical presentation and aetiology of HF

HF is a complex clinical syndrome characterised by reduced cardiac output and/or elevated intracardiac pressure, impairing the ability of the heart to function adequately and act as a pump to support physiological circulation (24, 25). HF symptoms may include shortness of breath with activity or when lying down, fatigue and weakness, swelling in the legs, ankles and feet, rapid or irregular heartbeat, reduced ability to exercise, wheezing, swelling of the belly area, very rapid weight gain from fluid build-up, difficulty concentrating or decreased alertness and chest pain, if heart failure is caused by a heart attack. HF results from myocardium injury caused by a wide range of pathologies including ischaemic heart disease (IHD), congenital heart defects, hypertension and non-cardiovascular (non-CV) systemic diseases such as diabetes and severe lung disease (28). More common aetiologies which affect more than two-thirds of cases includes IHD, hypertension (29), obesity, chronic obstructive pulmonary disease (COPD) and rheumatic heart disease (28, 29).

Classification

HF can be classified into acute and chronic in nature (24, 30). Acute HF is a life-threatening condition, with a rapid onset of HF symptoms whereas chronic HF refers to patients who have had HF diagnosis for at least three months and can be categorised into left or right ventricular failure (31).

The NYHA classification differentiates patients based on severity of HF symptoms (24) and it is commonly used for functional classification in patients with HF in clinical practice and as an entry criterion and/or outcome measure in clinical trials (Table). However, there are limitations to the NYHA classification, such as subjective interpretations from clinicians, poor prognostic value, and discordance between cardiologists in differentiating patients between class II and class III.

Table 4. NYHA functional classification based on severity of symptoms and physical activity

Classification	Description
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Abbreviation: NYHA, New York Heart Association.
Reference: (24).

Additionally, HF is categorised by LVEF. According to the 2021 ESC HF guidelines defined categories are:

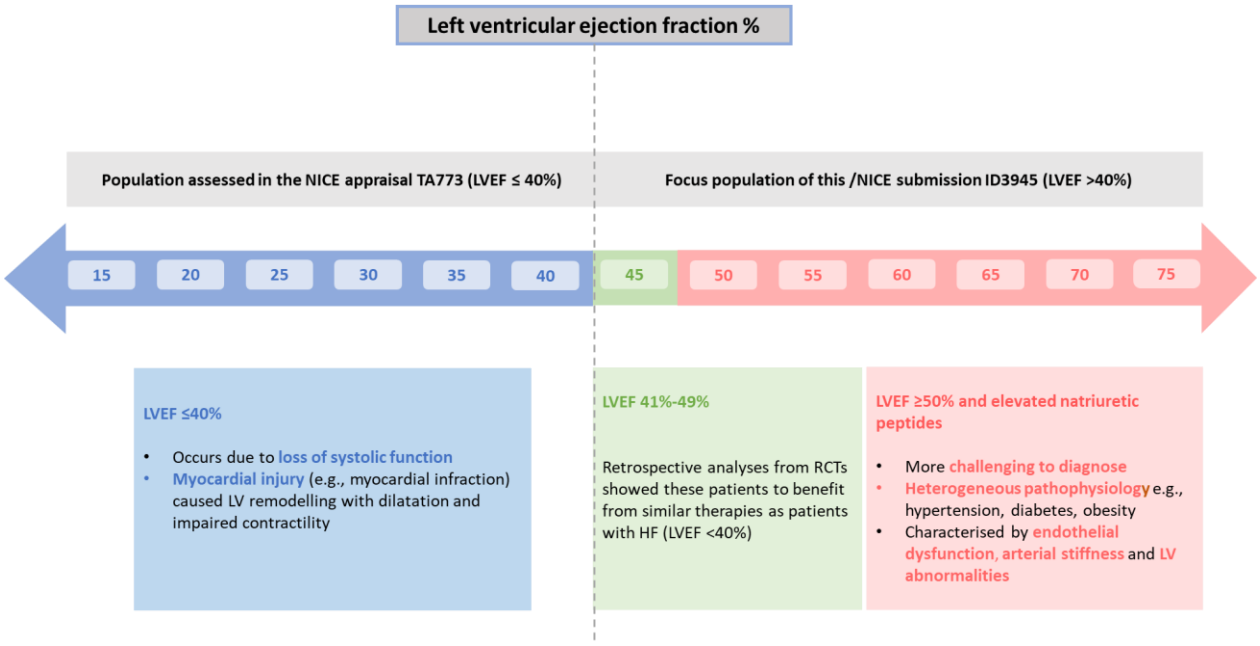
- HFrEF includes HF with LVEF ≤40%,
- HFmrEF (heart failure with mildly reduced EF) includes HF with LVEF 41% to 49%
- HFpEF (heart failure with preserved ejection fraction) includes HF with LVEF ≥50%.

However, there is ambiguity across the clinical community regarding the range of LVEF and the specific cut-offs used (39).

Therefore, for simplicity, this submission has defined the target population based on LVEF, (those with symptomatic chronic HF with LVEF >40%) (Figure 1), which focuses on the population not already assessed by NICE in TA773 (chronic HF with LVEF ≤40%). Therefore, the preferred outcome of this submission is to have a broad

recommendation for empagliflozin for all chronic HF patients in the NICE guideline NG106.

Figure 1. Left ventricular chronic HF



Abbreviations: HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; RCTs, randomised controlled trials.
Reference: (24).

B.1.3.1.2 Epidemiology

- In the UK, 920,000 people are estimated to live with HF and 200,000 people are newly diagnosed with HF every year (9, 32-34).
- Epidemiological data from registries in Western countries suggests that HFrEF affects approximately 50% of HF patients, whereas approximately 20–25% each have HFmrEF or HFpEF (35).
- The prevalence of HFpEF varies by country, although it is generally similar to or greater than the prevalence of HFrEF and HFmrEF (36-40).
- Studies demonstrate age-dependent increase in the prevalence of HFpEF; older age was strongly associated with new onset of HFpEF (35, 41, 42).
- The lifetime risk of HFpEF is reported to be similar between sexes, but women have a higher lifetime risk of HFpEF compared to that of HFrEF(43).

- The burden of HF is as high as other chronic conditions such as some types of cancer or COPD (13, 44).
- Coronary heart disease, diabetes and age are strongly associated with increased risk of HF
- Factors more likely to contribute to HFpEF include atrial fibrillation, diabetes and age, whereas cardiomyopathy and being male are the factors most likely to contribute to HFrEF(45, 46).

Prevalence and incidence

Approximately 64.3 million people worldwide are estimated to have HF (34). Based on 2014 data, there are more than 920,000 people with HF in the UK (13). From 2002 to 2014, the prevalence of HF in the UK increased by 23% (13), and the proportion of HF patients with LVEF >40% is increasing each year. A real-world evidence (RWE) study conducted in the UK (PULSE) reported that 8.7% of all HF patients had LVEF >40% in 2015, which was increased to 10.4% in 2019; however, this data should be interpreted with caution since a large proportion of patients had unknown LVEF in this RWE study (47).

Data on the prevalence of the different HF phenotypes stratified by EF (HFrEF, HFmrEF and HFpEF) are limited due to the lack of an ejection fraction (EF) assessment in numerous large-scale registries and administrative datasets. Epidemiological data across the EF spectrum are mostly derived from registries in Western countries, where HFrEF (EF <40%) seems to affect approximately 50% of HF patients, whereas approximately 20–25% each might have HFmrEF or HFpEF (35).

In European studies, the prevalence of HFpEF ranged between 18.0 to 65.4% whereas the prevalence of HFrEF and HFmrEF ranged between 16.3 and 63.0%, and 4.2 to 30.0% respectively (48-53). The prevalence of HFpEF varies by country, although it is generally similar to or greater than the prevalence of HFrEF and HFmrEF (36-40). Based on an HF registry from the United States, it is estimated that the

prevalence of HFrEF is 39%, 14% for HFmrEF, and 47% for HFpEF, whereas based on a Swedish HF registry, 56% of HF patients had HFrEF, 21% HFmrEF, and 23% HFpEF (35).

Community-based epidemiological studies and registries with LVEF assessments across the globe report the proportion of HFpEF as being between 19% and 55% of all HF patients. Multiple studies demonstrate age-dependent increase in the prevalence of HFpEF. Additionally, older age was also strongly associated with new onset of HFpEF (35, 41, 42).

The number of newly diagnosed HF cases in the UK has increased by 12% between 2002 and 2014 and there is no indication that the trend is slowing down (13). Around 176,000 to 200,000 people are newly diagnosed with HF each year in the UK, with the average age of diagnosis between 72 and 77 years (13, 32, 47). There has been a year-on-year increase in the incidence of HF since 2015. Recently published UK population data report an annual incidence of 0.12% in ages 55–64 years, rising to 1.2% in people aged > 85, which is equivalent to 63,000 new cases of HF each year (54).

Among incident HF cases between 2000 and 2010 in Olmsted County, the proportion of HFpEF increased over time (from 48% in 2000–2003 to 52% in 2008–2010), with women outnumbering men by 2:1. Furthermore, women experienced less decline in the incidence of HFpEF compared to HFrEF over 10 years (-27% versus -61%, respectively) (55). The lifetime risk of HFpEF is reported to be similar between sexes, but women have a higher lifetime risk of HFpEF compared to that of HFrEF (43).

Prioritising the improvement of outcomes for HF patients is as important as for other common conditions with a high burden of disease. The prevalence and incidence of HF in the UK is similar to the four most common causes of cancer combined (breast, prostate, lung and bowel) or COPD (13, 44). Hence, improving the healthcare for patients with HF is necessary given the high unmet need for these patients, which is particularly high for the 50% of all HF patients that present with LVEF >40%.

Comorbidities and risk factors

The cardio-renal syndrome (CRS) encompasses a spectrum of disorders of the heart and kidneys whereby the physiological interdependence of the two organs leads to their simultaneous, accelerated decline in a negative feedback cycle (56). Metabolic disturbances associated with diabetes can also lead to the pathogenesis of the CRS by causing biochemical, functional and morphological abnormalities of the heart and kidney (57). HF patients therefore often suffer from renal or metabolic comorbidities due to the overlapping risk factors for these conditions (58).

The prevalence of comorbidities is high among HF patients across the entire spectrum of LVEF(Table) (59). Nearly half of all HF patients have moderate to severe kidney dysfunction which increases the risk of hospitalisation or death compared to HF alone (14, 60, 61). Furthermore, nearly one-third have comorbid T2DM, also known to increase the risk of hospital admissions and cardiovascular (CV) death (14, 62). The onset of T2DM increases the risk of HF by two-fold in men and five-fold in women (63). Other common comorbidities related to HF are atrial fibrillation, valvular heart disease, IHD, hypertension and stroke (13, 24). Some non-CV comorbidities are thyroid disorder, obesity, anaemia and COPD (13, 24). A UK population-based cohort study showed that the patients with incident HF had high comorbidity burden, with 79% patients having at least three comorbidities (13).

The burden of comorbidities is much higher for HF compared to other common conditions, such as cancer. A retrospective Scottish study conducted between 2002 and 2011 on adults with HF and four of the most common cancers showed that 94.5% of HF patients had comorbidities compared to 62%-80% of patients with a cancer diagnosis.

Table 5. Common comorbidities in patients with HF

Medical History	HF (%)
Hypertension	67
IHD	49
Osteoarthritis	43

Medical History	HF (%)
Atrial fibrillation	40
Dyslipidaemia	28
CKD	24
Diabetes	22
COPD	19

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.
Reference: Conrad et. al. (2018) (13)

The major comorbidities associated specifically with HFpEF include atrial fibrillation, arterial hypertension, coronary artery disease, coronary microvascular dysfunction, renal dysfunction, T2DM, sleep apnoea, reduced lymphatic reserve, and the effects on oxygen utilization and physical activity (Table 6) (64). Atrial fibrillation is one of the most common precursors and predictors of the development of HFpEF. Conversely, if the arrhythmia is not already present, most patients with HFpEF are likely to develop it. If both HFpEF and AF coexist, the risk for worse outcomes increases exponentially, with a major increase in hospitalizations and a two- to three-fold higher mortality (65). Another common comorbidity in HFpEF patients is hypertension, which is diagnosed in approximately 75% of all HFpEF patients. Arterial hypertension causes myocardial remodeling and dysfunction in HFpEF patients through myocardial overload and systemic inflammation (66, 67). Coronary artery disease (CAD) is a common concomitant disease, detectable in more than 50% of HFpEF patients. When considering the prognosis of CAD, significant differences are seen in HFpEF patients compared with HFrEF patients. The risk of cardiovascular death, as well as the incidence of sudden death, is significantly higher in HFpEF patients with CAD compared with HFrEF patients with CAD (68, 69).

T2DM is a high-risk factor in patients with HFpEF and plays a significant role in diastolic dysfunction. Approximately one third of HFpEF patients have concomitant T2DM (70). Furthermore, T2DM has been described as a comorbidity with a high risk of mortality and hospitalization (71). T2DM causes functional, morphologic, and biochemical changes in the myocardium that can lead to diastolic dysfunction and

heart failure independent of other cardiovascular risk factors (72). HFpEF seems to be much more common in women than men in people with T2DM (73).

Table 6 Common comorbidities reported specifically for HFpEF patients

Major Comorbidities	% of HFpEF patients
Atrial fibrillation	21%
Arterial hypertension	5%
Coronary artery disease	50%
Renal dysfunction	30%
Diabetes Mellitus	45%
Sleep apnoea	48%

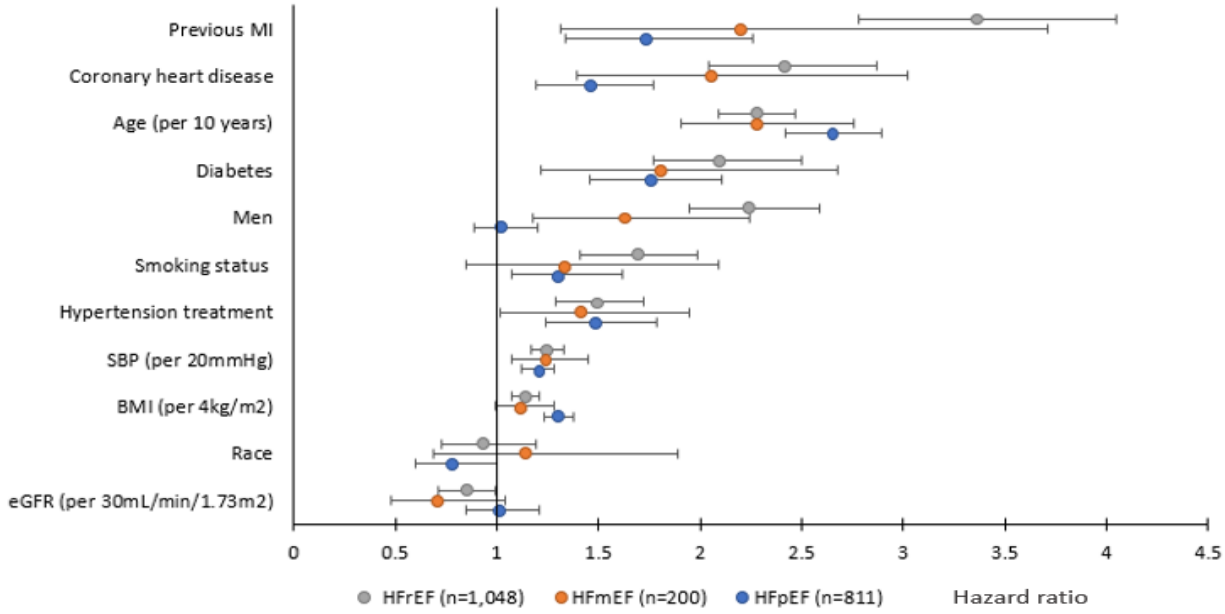
Abbreviations: HFpEF: Heart failure with preserved ejection fraction

Risk factors associated with chronic HF can be modifiable (e.g., diet and exercise) or non-modifiable (e.g., age, gender and comorbidities). Coronary heart disease, diabetes and age are strongly associated with an increased risk of HF (14). Hypertension, smoking, elevated body mass index (BMI), diet and poor physical activity are also contributing to the pathogenesis of HF (74-76).

Studies which specifically accessed the risk factors for HFrEF, HFmrEF and HFpEF reported several common clinical predictors like previous AMI, prevalent CHD, age, T2DM, cardiomyopathy, and smoking status (

Figure 2). From these, factors more likely to contribute to HFpEF include atrial fibrillation, diabetes and age, whereas cardiomyopathy and being male are the factors most likely to contribute to HFrEF (45, 46).

Figure 2: Multivariable-adjusted clinical predictors of incident HFrEF, HFmrEF and HFpEF using pooled data from four community-based longitudinal cohorts



Notes: HR represent hazard ratios of heart failure subtype associated with the presence vs absence of a dichotomous variable, or per increment in continuous variables as denoted in the figure. HR for ethnicity is a comparison of black vs white ethnicity. Multivariable-adjusted models include age, sex, ethnicity, SBP, hypertension treatment, BMI, diabetes mellitus, smoking status and previous myocardial infarction. Biomarker models include all clinical covariates plus individual biomarkers; eGFR = per 30 mL/min/1.73 m^2.

Key: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate HFmrEF, Heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure.

Source: Bhambhani V 2018 (45)

B.1.3.1.3 Disease burden

- Heart failure is a debilitating condition; the cardio-renal-metabolic (CRM) system-related comorbidities increases the symptom burden in HF patients (24, 77, 78).
- In the UK, HF mortality is variable and ranges between 14.4% and 26% at one year and between 48.5% and 68.1% at five years (79-82).

- Comorbidities, such as chronic kidney disease (CKD), T2DM and lung disease lead to an increased number of hospitalisations and in turn are associated with an increased risk of mortality (79-82).
- In patients with HFpEF, comorbid conditions such as lung disease, obesity, and frailty may contribute to symptom burden and may limit the accuracy of the physical examination for assessment of volume status and prognosis.
- An increasing number of comorbidities are associated with a significantly higher risk of 1-year mortality for patients with chronic HF, with a stronger association observed for HFpEF compared with HFrEF.
- HF is associated with a high rate of hospitalisation, especially in elderly patients (81, 83-86). There is an unmet need to lower the hospitalisation rates and reduce the risk of mortality for chronic HF patients (86).

Symptomatic burden

HF patients experience debilitating symptoms including breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue and ankle swelling (24, 77). The interdependencies within the CRM system lead to accelerated progression of CKD and HF and this increase the symptomatic burden on HF patients (78). Around a quarter of HF patients develop T2DM and up to 50% of these patients develop CKD (78). Furthermore, there are challenges in diagnosing chronic HF in terms of availability and use of echocardiography services (87, 88). Access to echocardiography, shortage of technically trained staff and complexity of symptoms usually cause delay in commencement of treatment in HF patients (87, 88). This means that HF patients are at a high risk of decompensation or cardiac event such as breathlessness, severe peripheral oedema and chest pain (33).

With no universally accepted diagnostic guideline, many HFpEF patients continue to be misdiagnosed or underdiagnosed. It is complicated to diagnose HFpEF patients because they have a normal ejection fraction and present with non-specific symptoms such as dyspnoea or exercise intolerance caused by numerous other non-cardiac conditions, such as chronic lung disease, anaemia, and CKD (89, 90). Furthermore, in patients with HFpEF, comorbid conditions such as lung disease, obesity, and frailty

may contribute to symptom burden and may limit the accuracy of the physical examination for assessment of volume status and prognosis (91).

Morbidity and mortality

There remains a high unmet need to reduce the risk of mortality in all chronic HF patients. The prognosis of HF remains poor and the burden of HF in the UK is similar in magnitude to that of the four most common cancers (breast, prostate, lung and bowel) combined (13, 79, 81). Estimates for 1- and 5-year HF mortality in the UK are variable, but range between 14.4% and 26% for 1-year and between 48.5% and 68.1% for 5-year post-diagnosis (79-82). A population-based cohort study in the UK estimated the 10-year mortality for HF patients to be 75.5% (80). A UK retrospective study of 241 people (41 with chronic HF [LVEF >40%]) indicated that 27% of patients with chronic HF (LVEF >40%) died within 1 year of hospital admission (92). IHD was a significant predictor of mortality among these patients (hazard ratio [HR] 7.14; 95% confidence interval [CI], 1.51 to 33.85; p=0.01) (92).

The reasons for CV mortality and non-CV mortality in patients with HF are varied, and the risk of death is significant across the EF spectrum, although some differences have been reported. Published literature reported that most deaths in HFpEF patients are CV-related (60%-70%), but also the proportion of non-CV deaths among all deaths are higher in patients with higher LVEF (93, 94). Common reasons for CV mortality in HFpEF patients are sudden cardiac death (around 40%), worsening HF (20%-30%), and myocardial infarction (MI) and stroke (5%-15%) (94). For non-CV deaths, cancer (30%-40%) followed by infection/sepsis (around 25%) are most reported (94). Studies show greater burden from non-CV comorbidities in HFpEF compared with HFrEF, also suggesting a higher proportion of non-CV causes of death in HFpEF (95, 96). This attributes to non-CV conditions such as DM, kidney failure, anaemia, and obesity as drivers of disease, poor prognosis and increased risk of mortalities. The probability of a non-CV death increases in both HFpEF and HFrEF with advancing age, but it is greater in the HFpEF patient category (95, 96).

Compared to other European countries, mortality outcomes for HF patients in the UK appear worse, as significantly higher mortality rates have been observed in the UK, based on RWE studies (97-99). These studies reported a 1-year mortality rate ranging

from 6.4% to 20.0% in chronic HF patients and a 5-year mortality rate of 45.0% in chronic HF patients (47, 97-99).The risk of all-cause mortality at 1-year follow-up was significantly higher in HFrEF patients with worsening heart failure (WHF) than in HFrEF patients without WHF. Significant predictors ($p < 0.05$) of in-hospital mortality in patients who have either HFpEF or HFrEF are hypertension, sepsis, prior stoke, septic shock, and CKD. Obesity was associated with significant ($p < 0.05$) lower in-hospital mortality in HFrEF but not in HFpEF (36, 100).

The overall prognosis of HF patients is exacerbated when patients have other comorbidities including CKD, T2DM, atrial fibrillation and obesity (101-103). The presence of diabetes and CKD in HF patients is associated with increased mortality and hospitalisation (60, 78). A UK study reported that in patients who have both HF and CKD, hospitalisation and mortality rates increased by 11% and 17%, respectively, compared to HF patients who do not have CKD (104). Furthermore, HF patients with T2DM showed a higher mortality rate of 34% compared to those without T2DM with a mortality rate of 22% from either a CV death or HHF (102).

Many comorbidities significantly increase the risk of all-cause mortality in patients with HFrEF and/or HFpEF including diabetes, COPD ($p < 0.001$), renal insufficiency ($p < 0.01$), anaemia ($p < 0.01$), dementia ($p < 0.01$), liver disease ($p < 0.05$) and cerebrovascular accident ($p < 0.05$)**.** An increasing number of comorbidities are associated with a significantly higher risk of 1-year mortality for patients with chronic HF, with a stronger association observed for HFpEF compared with HFrEF ($p = 0.02$) (105-107).

Healthcare system burden

There is an unmet need to lower the hospitalisation rates and in turn reduce the risk of mortality in chronic HF patients, as HF is the most common cause of hospitalisation in patients over 65 years of age (81, 83-86). A 2014 study from the UK suggested that approximately 20% of patients hospitalised with HF have an LVEF ≥50% (108). A global study, including UK patients, found that over a median follow-up of 4.1 years, the AC hospitalisation rate was 56.5% among all patients with chronic HF (LVEF

≥45%) (102). A hospital readmission rate of 20% was also reported in the 12 months after discharge for patients with chronic HF (LVEF >40%) in the UK (92).

There are several factors contributing to the increased risk of hospitalisation and rehospitalisation. A recent Clinical Practice Research Datalink (CPRD) study identified that 80% of HF cases in England are diagnosed after emergency hospital admission for acute HF symptoms (109). The burden of hospitalisation is significant across the LVEF spectrum; however, some differences have been observed. Higher rates of HHF are observed in HF patients with diabetes, where the readmission rate is nearly double compared to those without diabetes (71, 110, 111). Furthermore, in patients with chronic HF (LVEF >40%), the challenges in diagnosis and limitation of available treatment for its management contribute to the increased risk of hospitalisations and mortality (24, 33).

B.1.3.1.4 Economic burden

- HF accounts for 2% of the total NHS budget annually (112).
- The economic burden of HFpEF has been shown to increase over time. The costs associated with an initial hospitalization are significant in patients with HFpEF (113).
- The economic burden increases even further in those patients with HF and comorbidities (114, 115). The presence of T2DM in patients with HFpEF and HFrEF increases both length of stay and hospitalisation costs (115).
- In the UK in 2012, the direct and indirect costs of HF amounted to £2.0 billion and £888 million, respectively (87, 112, 116, 117).
- There is a need to reduce HHF costs, considering its major contribution towards total HF costs in the UK.

There is a substantial economic burden of HF in the UK, where it is estimated to annually account for 2% of the NHS budget, with 60% to 70% of the costs related to hospitalisations (116, 117). HF patients accounted for 1 million inpatient bed days (representing 2% of all NHS inpatient bed days and 5% of all emergency medical

hospital admissions), with an average length of stay of 6 to 9 days and a 3 -month readmission rate of 25% (112, 118).

A US retrospective study assessing trends in the rates of hospital discharges and related costs in patients with HFpEF between 2009 and 2016 demonstrated that the continuing increase in the economic burden due to HFpEF is in line with the ageing of the general population and the inadequacies of available treatment options for patients with HFpEF. Among patients with HFpEF, there was a 13.0% increase in the rate of discharges, as well as 33.0% increase in hospital charges and 102.0% increase in total charges between 2009 and 2016 (119). A similar finding was reported in a systematic literature review conducted to assess the economic burden of hospitalisation in patients with HFpEF between 2001 and July 2020. The cost of hospitalisation accounts for approximately 80% of total costs of HFpEF treatment (113).

The economic burden increases even further in HF patients with comorbidities. Notably, in HF patients, the burden of CRM-related conditions is substantial in terms of the cost burden and AC hospital admissions and this is further amplified in the T2DM population (114). The presence of T2DM in patients with HFpEF and HFrEF increases both length of stay and hospitalisation costs compared to those without T2DM (115).

The cost associated with hospitalisation is the main driver of UK healthcare spending for HF patients; hence, the reduction of hospitalisation frequency and duration would significantly lower the overall economic burden of HF to the NHS. In 2012, it was estimated that the direct and indirect costs of HF amounted to ~ £2.0 billion and £888 million, respectively (112, 116, 117). During the last three months of a HF patient's life, the inpatient care or critical care account for more than 90% of healthcare costs (120). Although not a direct cost to the NHS, the indirect cost of informal care cost has also shown to rise with increasing rates of hospitalisation (121-123). It is important to note that the broader societal costs of hospitalisation may be even higher as informal care has further shown to significantly impact both the caregiver's leisure time and productivity; evidence suggest that caregiving responsibilities result in an average of 28 hours per week of time commitment (121-123).

B.1.3.1.5 Humanistic burden

- HF has a substantial impact on patients' HRQoL, affecting their physical, social, emotional and psychological well-being (33).
- The impact of HF on the HRQoL of carers is also significant (123).

HF has a significant impact on patients' physical well-being across the EF spectrum. Some differences have been reported in quality of life across the EF; however, there is no consensus in the published literature. The physical well-being of HF patients was reported in several UK studies, where patients experienced a range of symptoms including breathlessness, reduced sleep quality, frailty, cognitive/psychomotor impairment, respiratory symptoms and chest pain (24, 77, 124). One UK study reported a continuous quality of life difference in chronic HF patients compared to those without HF, where on an average, a 16% reduction in physical activity was observed (124). Another UK study showed that a higher proportion of patients with chronic HF (LVEF >40%) experienced a reduction in daily activities compared to those without HF (52.2% *versus* 36.8%) (77).

The impact of HF on patients' emotional well-being is substantial across the EF spectrum. Patients have often reported feeling overwhelmed, frustrated, limited and worried, particularly around the caring for their children/spouses and the impact it has on their self-confidence (33). The substantial reduction in patient's physical and emotional well-being are even associated with a higher risk of mortality (77, 124).

Similarly, the impact of HF on the quality of life of carers is also significant. Carer's health as a result of carer's responsibilities were also shown to be significantly impacted by stress (35%), moderate to severe anxiety/depression (32%), emotional strain (33%), physical (33%) or mental (31%) tiredness and pain/discomfort (29%) (123).

B.1.3.2 Clinical pathway of care

- The NICE guideline for chronic HF in adults (NG106) recommends diuretics, calcium-channel blockers, amiodarone (in consultation with a specialist) and anticoagulants for the management of all patients with chronic HF; however,

there were no recommended targeted pharmaceutical treatments for chronic HF (LVEF >40%) at time of its publication (9).

- For patients with chronic HF (LVEF >40%), until recently treatment was focused on the management of comorbidities such as hypertension, atrial fibrillation, IHD and diabetes in line with NICE guidance (9) as well as symptomatic relief of congestion symptoms through diuretics.
- In clinical practice, the implementation of NG106 for HF patients is highly variable (9, 79). This is observed more acutely in those patients with a higher LVEF, due to challenges in diagnosis (125, 126).
- Therefore, an unmet need to support implementation of guideline-directed care and earlier diagnosis of HF, especially in those with an LVEF >40% remained.
- Recently, dapagliflozin was recommended by NICE, within its MA, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902).
- Empagliflozin is anticipated to be positioned in the same place in the clinical treatment pathway as dapagliflozin.
- Thus, empagliflozin represents an additional SGLT2 treatment option that would offer healthcare professionals and patients an additional treatment choice in the management of this debilitating condition.

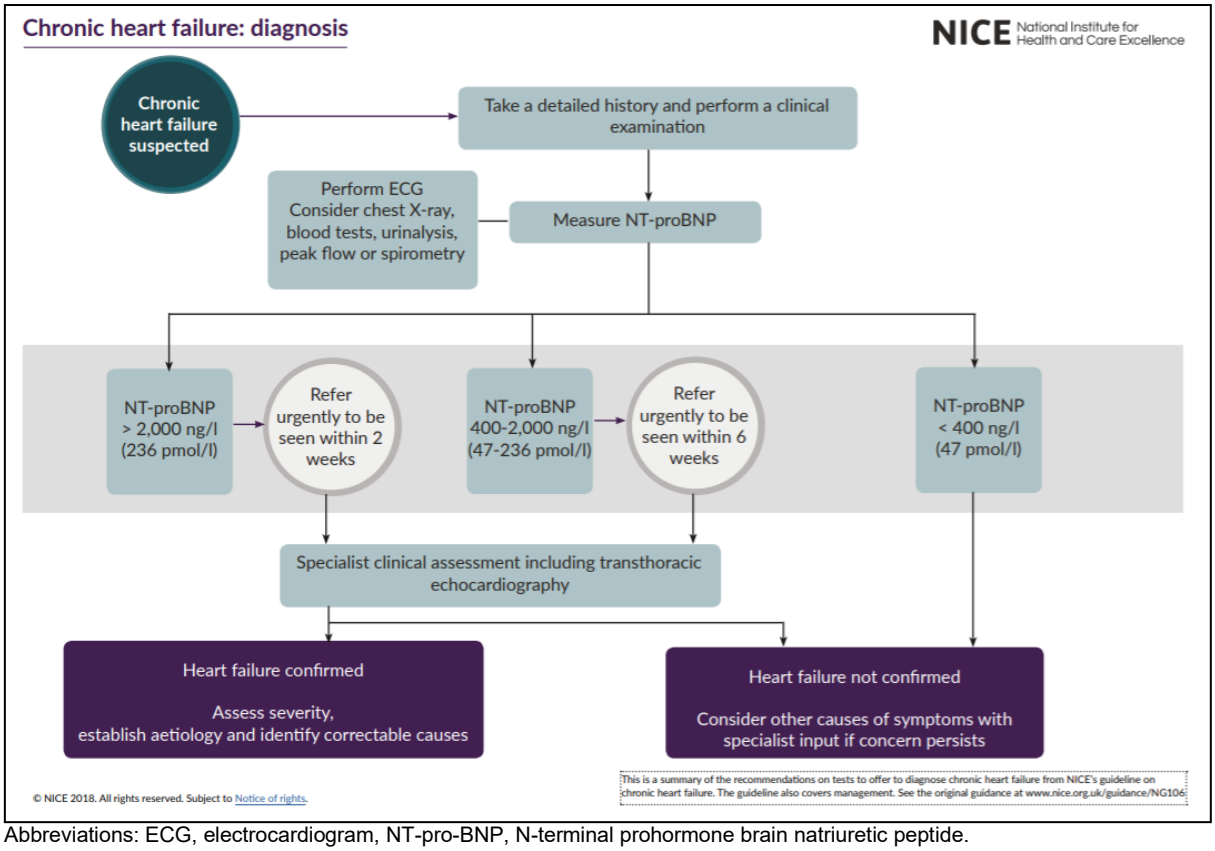
B.1.3.2.1 Current standard of care

NICE clinical treatment pathway

The diagnosis of HF is multifactorial and encompasses detailed clinical history, physical examinations, electrocardiograms (ECGs), echocardiography, stress tests, chest x-rays, coronary angiograms, cardiac computerised tomography (CT) scans, magnetic resonance imaging (MRI), myocardial biopsies and laboratory tests. Given the uncertainties that are intrinsic to a clear diagnosis of HF on physical examination alone, and the outcome for patients left undiagnosed, the NICE and ESC guidelines recommend testing of serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) in people with suspected HF as an essential diagnostic tool (Figure 3) (9, 24). However, the NT-pro-BNP level cannot differentiate between chronic HF LVEF ≤40% and LVEF >40% (9). Transthoracic echocardiography is required for confirmatory

diagnosis and to inform classification of HF, which in turn guides the management of the condition (9, 24).

Figure 3. Chronic HF diagnostic pathway



Abbreviations: ECG, electrocardiogram, NT-pro-BNP, N-terminal prohormone brain natriuretic peptide.
Source: NICE guideline NG106 (9)

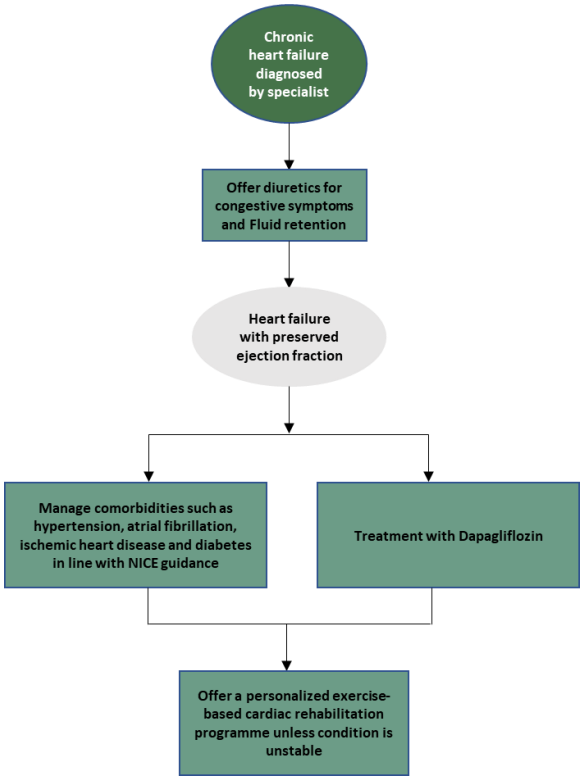
Following chronic HF (LVEF >40%) diagnosis, the treatment focuses on the management of comorbidities and to alleviate symptoms and improve well-being (97, 127). The latest NICE guidelines did not recommend any specific therapy for the treatment of chronic HF (LVEF >40%), as no evidence-based treatment existed (Figure 4) at time of its publication (9).

Calcium-channel blockers, amiodarone (in consultation with a specialist), anticoagulants and diuretics can be used for the management of patients with chronic HF (dependent on symptoms and associated comorbidities) (9). Diuretics are used routinely to provide symptomatic relief, particularly in the presence of oedema, but without direct evidence of survival benefit (128). Additionally, the efficacy benefit of diuretics across the LVEF spectrum of HF is not equal (9, 128). Patients with chronic

HF (LVEF >40%) are usually offered a low to medium dose of loop diuretics such as furosemide (<80 mg per day) (9). Patients who do not respond to diuretics are then referred to a specialist who can optimise comorbidity management and can advise patients to use other services, including cardiac rehabilitation, services for older people and palliative care services, as needed (9).

Dapagliflozin was recently recommended by NICE, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902). The recommendation for dapagliflozin was supported by evidence from a randomised, double-blind, phase 3 clinical trial (DELIVER) (10). Dapagliflozin plus background therapy for symptom management was found to reduce the combined risk of cardiovascular mortality or HHF (i.e., primary outcome) compared with placebo plus standard care. Furthermore, dapagliflozin demonstrated a trend to reduce the likelihood of mortality from cardiovascular or other causes, but the results of the DELIVER trial were not statistically significant.

Figure 4. NICE treatment pathway for chronic HF (LVEF >40%). Dapagliflozin was recently recommended by NICE, as a treatment option and will be included in the treatment pathway.



Note: As per NICE guideline, all patients with LVEF <40% are classified as HFrEF and remaining other HF patients are classified as HFpEF.
Abbreviation: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Source: Adapted from NICE guideline NG106, 2018 (9)

Clinical practice and HF services

The 2021 ESC guideline recommended similar treatments for management of patients with chronic HF; LVEF <40% or LVEF 41% to 49% (Table 7) (24). However, the strength of the recommendations are low for patients with LVEF 41% to 49% and were not supported by evidence as no substantial prospective randomised controlled trials (RCTs) have been exclusively conducted in patients with LVEF 41% to 49% (24). The guideline does not recommend any specific medications for patients with chronic HF (LVEF ≥50%), as the relevant evidence was not available at the time of its publication (24). The management of these patients was limited to screening and treatment of CV and non-CV comorbidities (24). In clinical practice, the prescription of pharmacological treatments in patients with chronic HF with LVEF >40% was similar to that with LVEF ≤40% since there were no evidence-based guidelines for these patients (129, 130). The treatments recommended in NICE guidelines, which should reflect the treatment offered in clinical practice, will now include dapagliflozin on top of background therapy for symptom management.

Table 7. Recommendations or pharmacological treatments to be considered in patients with chronic HF based on 2021 ESC guideline

LVEF ≤40%	LVEF 41%-49%	LVEF ≥50%
All patients: • An ACEI • A beta-blocker • An MRA • Dapagliflozin or empagliflozin • ARNI **Selected patients:** <u>In patients with congestion</u> • Diuretics In patients who are unable to tolerate or remain symptomatic despite	**All patients:** • An ACEI • A beta-blocker • An MRA • ARNI **Selected patients:** <u>In patients with congestion</u> • Diuretics	• Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities • Diuretics

LVEF ≤40%	LVEF 41%-49%	LVEF ≥50%
treatment on ACEI (or ARNI), a beta-blocker and an MRA • An ARB • Ivabradine • Vericiguat • Hydralazine and isosorbide dinitrate • Digoxin	In patients who are unable to tolerate or remain symptomatic despite treatment on ACEI (or ARNI), a beta-blocker and an MRA	

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists.
Reference: (24).

Many challenges are faced by GPs in managing patients with chronic HF in primary care. GPs reported limited understanding of different types of HF, mostly due to a lack of clear consensus on its definition and diagnosis (126). Patients with chronic HF, regardless of their LVEF, present in clinical practice in the same way (131). Both associated CV and non-CV comorbidities make the diagnosis very complex (131). Primary care often test for elevated NT-proBNP, and if HF is suspected, the patient is referred to specialist care where the diagnosis and type of HF is confirmed (125). However, echocardiograms are unreliable for some of the arbitrary definitions for HF subtypes (e.g., distinguishing between an LVEF of 40% to 45%) and do not often report an exact value for LVEF >55% in clinical practice as it would be classed as “normal EF” (125). There are limitations in access to echocardiography and technically trained staff as well. Variation has been observed in access to natriuretic peptide testing for diagnosis and monitoring and use of validated tools to quantify the severity of symptoms (79, 88). Combined, these factors lead to delays in diagnosis and subsequently, in the commencement of treatment.

There are inconsistencies between the guidelines and clinical practice in HF service settings (e.g. hospital-based, community-based, hospital- and community-based or hospital with community work) (9, 79). Optimal management of chronic HF requires optimisation of pharmacological treatment, nursing support and treatment of comorbidities, and should be delivered by a multidisciplinary team (MDT) (9, 79). In UK clinical practice, however, the structure and provision of HF care varies and is not

always in accordance with the current guidelines (9, 79). There is a lack of availability of specialist services for patients with chronic HF with higher LVEFs (132). Around 60% to 80% of specialist HF practices reported patients with LVEF >50% and only 53% of community services reported these patients of LVEF >50% (79, 132). Thus, the patients with LVEF >50% are usually discharged to primary care after diagnosis, who then take the lead in managing these patients (88, 133).

The COVID-19 pandemic has further negatively impacted the availability of HF services, including diagnostic and outpatient specialist care services. Patients are now also less likely to seek medical care for any HF symptoms they experience (19). A UK-based study reported that in primary and secondary care, inpatient ECGs reduced by 44% and NT-proBNP tests reduced by 75% during the COVID-19 lockdown period (134). This led to a reduction in patients presenting with signs and symptoms of HF and a 34% decrease in the number of new patients referred to community HF service (134). Many HF specialist clinicians had to be reallocated to acute or medical wards in order to accommodate COVID-19 patients (134-136). Home visits and in-clinic appointments were postponed for around 65% of HF patients, and telephone or video consultation services increased by 66% (134, 137).

COVID-19 has exacerbated pre-existing health inequalities, as patients in a lower socio-economic group were already less likely to seek medical attention in secondary care before the pandemic. HF is also a risk factor for worse outcomes with COVID-19 (138, 139), and patients with chronic HF were 17% more likely to die of COVID-19 than those without chronic HF (140). Additionally, HF patients with a lower socio-economic status were already more likely to have worse CV outcomes than those with a higher socio-economic status (13).

B.1.3.2.2 Unmet need

- Patients with chronic HF continue to experience high mortality and morbidity, high symptom burden, reduced functional capacity and poor quality of life (13, 24, 77, 79, 109).

- Until recently no therapy has demonstrated efficacy for HF across the broad spectrum of LVEF (112).
- Prescribed drugs for HF across the broad spectrum of LVEF (e.g. ACEI/ARB, beta-blockers, or MRAs) are generally used to control CV comorbidities, but they have not demonstrated benefit for patients with HF and LVEF>40% and have not received MA approval (24).
- Dapagliflozin was recently recommended by NICE, within its MA, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902). Access to both empagliflozin and dapagliflozin addresses the unmet need for evidence-based treatment options for patients across the HF spectrum and would provide healthcare professionals and patients with the option to choose between two licensed treatments.

As discussed in earlier sections, the mortality and morbidity of HF remain high due to a number of factors, including late diagnosis that most often occurs after emergency admission for acute HF symptoms, lack of pharmacological therapy and widening socio-economic inequalities (13, 79, 109). Further, with each subsequent hospitalisation, the risk of death increases (141, 142). During 2018-2019, there were more than 100,000 hospital admissions for HF in the UK, an increase of almost a third compared to 2013-2014 (143, 144). The challenges in diagnosis and limitation of available treatment for its management contribute to the increased risk of HF hospitalisations and mortality (24, 33, 88). The HRQoL of patients was also markedly reduced especially in patients with chronic HF (LVEF >40%) since there were no licensed efficacious treatments targeting this population (24, 77).

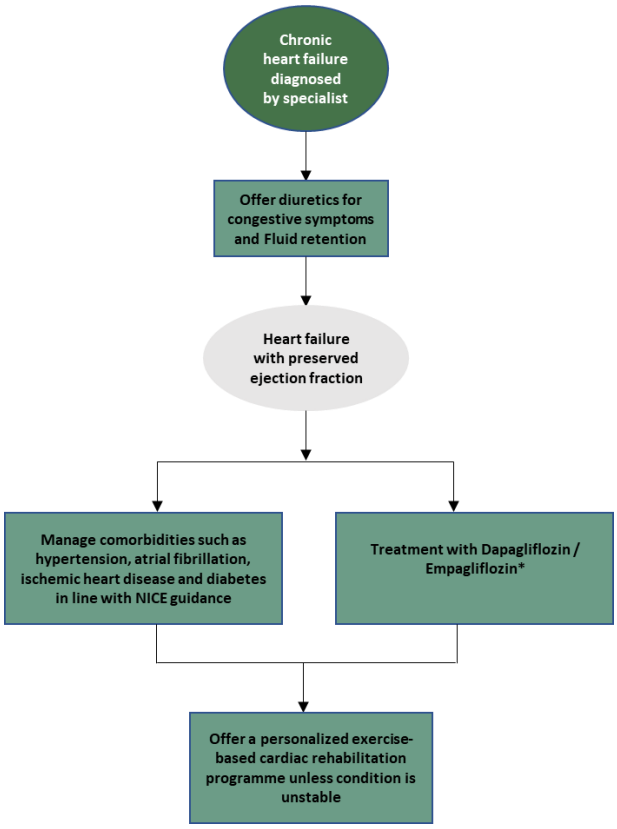
The recent recommendation of dapagliflozin by NICE offers chronic HF patients with preserved or mildly reduced EF (i.e., LVEF >40%) for the first time an evidence-based treatment option consisting of an SLGT2 inhibitor on top of background therapy for symptom management (TA902). Access to both empagliflozin and dapagliflozin as an SGLT2 inhibitor option on top of background therapy addresses the historically high unmet need for evidence-based treatment options for patients across the HF spectrum, and would provide healthcare professionals and patients with the option to choose between two licensed treatments.

B.1.3.2.3 Positioning of empagliflozin in the UK treatment pathway

- Empagliflozin was the first MHRA approved therapy for patients with HF and LVEF >40%, later followed by MHRA approval for dapagliflozin, to demonstrate efficacy in a broad range of chronic HF patients across the full spectrum of LVEF (4, 5).
- Empagliflozin as an add-on to background therapy for symptom management leads to a significant reduction in the risk of CV death or HHF, and a sustained improvement in renal outcomes and HRQoL compared to background therapy alone in patients with chronic HF (LVEF >40%) (4).
- Recommendation of empagliflozin for patients with chronic HF (LVEF >40%) provides the opportunity to maximise outcomes for these patients who have a historically high unmet need, and also allows patients a choice between two licensed available treatment options.

Based on the population studied in the pivotal phase III study EMPEROR-Preserved, the optimal positioning for empagliflozin in the NICE pathway is as initial treatment for chronic HF (LVEF >40%) patients. Efficacy and safety demonstrated for empagliflozin in the EMPEROR-Preserved trial (4, 5) indicates that empagliflozin should be positioned after diagnosis of chronic HF (LVEF>40%) (Figure 5).

Figure 5. Proposed positioning of empagliflozin in NICE treatment pathway for chronic HFpEF



*Proposed positioning of empagliflozin in NICE treatment pathway as dapagliflozin.

Note: As per NICE guideline, all patients with LVEF <40% are classified as HFrEF and remaining other HF patients are classified as HFpEF.
Abbreviation: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Source: Adapted from NICE guideline NG106, 2018 (9)

In a combined HF analysis of EMPEROR-Reduced and EMPEROR-Preserved stratified by LVEF, empagliflozin reduced the risk of CV death or HHF, mainly by reducing HF hospitalisations in chronic HF patients (145). The magnitude of the effect of empagliflozin on HF outcomes was similar in all HF patients irrespective of EF (145). The EMPEROR-Preserved trial showed that empagliflozin has the potential to provide additional efficacy in combination with any given background therapy in patients with chronic HF (LVEF >40%) (4, 146). The composite primary outcome in the EMPEROR-Preserved study showed that 13.8% of patients receiving empagliflozin plus background therapy *versus* 17.1% receiving background therapy alone experienced

either a HHF or CV death event (HR 0.79; 95% CI, 0.69 to 0.90; p=0.0003). The decline in renal function, evaluated based on change in eGFR slope from baseline, was significantly slower in the empagliflozin group, with an estimated difference in slope of about 1.36 mL/min/1.73 m^2 per year *versus* placebo (95% CI, 1.06 to 1.66; p<0.0001). The results from the adverse events (AE) and safety laboratory analyses in the EMPEROR-Preserved study were similar to the known safety profile of empagliflozin and no new occurrences were identified. Empagliflozin has an established safety profile and does not show any relevant drug-drug interactions (4). Further benefits of empagliflozin are that it is a once-daily dose without the need of any dose titration and thus, no additional clinical time is needed to optimise a patient's treatment (4); it does not have a significant effect on patient's potassium levels and blood pressure; and it does not need additional renal monitoring beyond usual care (4). Empagliflozin has demonstrated improvement in HF-related outcomes across a broad range of chronic HF (LVEF >40%) populations including the presence or absence of T2DM and/or CKD, and baseline health status as measured by KCCQ (4). Empagliflozin has shown similar efficacy results among patients with chronic HF (LVEF ≤40%) in the EMPEROR-Reduced trial which has been summarised in a previous NICE submission TA773 (1).

A NICE recommendation for empagliflozin in chronic HF across a broad range of EF will likely have a positive impact on the existing pathway. The experience of GPs in prescribing SGLT2i for T2DM and there being no requirement for dose adjustment should facilitate initiation of empagliflozin in chronic HF patients within primary care (147). Currently, HF patients are treated based on their LVEF, which is determined through echocardiograms (24). It has been seen that echocardiograms can be unreliable and thus, depending on the result can lead to some patients not being referred or not receiving the guideline-directed treatment (33, 125). With empagliflozin, all patients diagnosed with HF have the opportunity to receive an evidence-based targeted treatment, regardless of LVEF. Additionally, the administration schedule of empagliflozin (10 mg tablet once daily) is convenient for patients and does not require any additional monitoring beyond usual care (23).

Since dapagliflozin was recently recommended by NICE as an SGLT2 inhibitor treatment option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902), it is the only comparator of interest for empagliflozin.

B.1.4 Equality considerations

Socio-economic inequalities in CV disease present a major and persistent UK public health challenge. The UK-based population studies demonstrate that socio-economic deprivation is a strong risk factor for the development of HF and adverse HF outcomes (13, 14). Individuals in the lowest socio-economic group are 1.61 times more likely to experience incident HF than the most affluent individuals and on an average, at a 3.5 years younger age with a greater comorbidity burden at time of HF symptom onset (13). Furthermore, the socio-economic status is associated with a diverging trend of HF outcomes in England, whereby patients from the most deprived group have a significantly higher risk of AC (HR, 1.17; 95% CI,1.14 to 1.21) and CV mortality (HR, 1.18; 95% CI, 1.14 to 1.23) than the most affluent ones (143).

Since the early 2000s, the socio-economic gradient in HF incidence and outcomes have been widening:

- The mean age at diagnosis increased by 2.45 years (95% CI, 1.58 to 3.32) among the most affluent but tended to decrease among the most deprived (13).
- The annual risk in HHF has increased by 1.6% (95% CI, 0.6 to 2.6) for the most deprived compared to a stable risk for the most affluent group (143).

The inequality in access to specialist care in the UK may be one of the drivers of the observed trends in HF. England-based socio-economic studies have shown that after controlling for need, more affluent individuals tend to consume more public and private specialist visits, but not general practice visits, than those from a lower socio-economic class, and experience significantly shorter waiting times for a coronary revascularisation procedure at the same public hospital (15, 148). The prominent role of a secondary care specialist in all aspects of HF care (including diagnosis, management and initiation of new medicines) that can only be accessed upon referral from a GP, could therefore be contributing to the observed socio-economic disparities in clinical characteristics and outcomes of HF (9).

The choice of setting for empagliflozin initiation in primary care or under specialist supervision is thus a highly pertinent public health issue. Appropriate prescribing of empagliflozin across primary and secondary care can support the reduction in disparity in terms of access to HF care across socio-economic groups within the UK. This is because empagliflozin has the potential to improve CV outcomes and slow renal decline in chronic HF (LVEF >40%) patients in an early, sustained manner and prevent HHF (4). Empagliflozin significantly reduced worsening of an HF event (CV death, HHF or an emergency or urgent HF visit requiring intravenous treatment) 18 days after randomisation and maintained significance thereafter (149). It was the first treatment that can simultaneously provide cardiac and renal benefits to chronic HF patients across broad range of LVEF including patients with comorbid diabetes and/or severe renal impairment (eGFR 20 to 30 mL/min/1.73 m^2), which are more likely to coexist in the most deprived patients (14). Additionally, patients treated with empagliflozin do not show any relevant drug-drug interactions, have a once-daily dose and do not need additional renal monitoring beyond usual care (4). Limiting initiation of empagliflozin to secondary care specialists could lead to a delayed and/or lower uptake of empagliflozin among the most socioeconomically disadvantaged groups as they consume fewer specialist visits and present to healthcare providers at a later stage of illness (148). Delayed exposure to the benefits of SGLT2 inhibition may in turn widen the existing divide in HF outcomes between socio-economic classes in England.

The recent COVID-19 pandemic has led to significant disruption in the provision of all types of cardiology services including outpatient and community HF services (134). Patterns of past care suggest that the elderly and those living in deprived areas are most likely to be disproportionately affected by increased waiting times for cardiology appointments (15, 150). With a condition that has a 1-year mortality of approximately 24% and being the leading cause of hospital readmissions, a long wait for a HF specialist appointment may have grave consequences for socioeconomically disadvantaged HF patients in England (80).

In addition to recently recommended dapagliflozin, access to reimbursement for empagliflozin will provide more than one treatment option for patients with symptomatic chronic HF with preserved or mildly reduced EF. Moreover, it will also

provide an alternative treatment option for dapagliflozin-intolerant patients. This in turn will support the overarching goal of reducing inequity in access to care for HF patients, in line with NICE's Social Value Judgements, pillar 3 of NICE's new 5-year strategy (17, 18) and the conclusions from the Marmot COVID-19 Build Back Fairer review (19).

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Dapagliflozin, as described in the NICE TA902, is the only relevant comparator for this health technology appraisal, as it addresses the same decision problem of treating chronic HF patients with preserved or mildly reduced EF (i.e., HF with LVEF >40%) using similar mechanism of action (NICE TA902) (8). Empagliflozin and dapagliflozin are the only two licenced treatments for this indication.

Clinical outcomes

Most HF trials have used a composite endpoint of death and hospitalisations (i.e., CV mortality or HHF) as the primary endpoint (151). Single endpoints that are typically included in HF trials are CV mortality, AC mortality, and HHF. All those endpoints (i.e., composite and single endpoints) were included in the evidence presented in the NICE TA902, derived from the DELIVER trial (Table 8) (8, 10). The committee concluded that dapagliflozin significantly reduced the combined risk of CV mortality or HHF (152). These endpoints were also reported in the EMPEROR-Preserved trial, and this overlap facilitates an ITC between empagliflozin and dapagliflozin, as detailed in section B.3.9.

The DELIVER trial showed that dapagliflozin trended to a reduction in AC mortality (HR 0.94, 95% CI 0.83 to 1.07) and CV mortality (HR 0.88, 95% CI 0.74 to 1.05) compared with placebo, although neither outcome was statistically significant in favour of dapagliflozin as the DELIVER trial was not powered to assess the impact of dapagliflozin on AC and CV mortality. The economic model in the NICE TA902 includes a treatment effect on both CV and AC mortality as the base case and provides scenario analyses where treatment effect is excluded (i.e., the risk for CV and AC mortality is the same for dapagliflozin and placebo). Removing the treatment effect for mortality increased the ICER; the committee concluded that this is an overly pessimistic scenario and that it is likely there is a direct and/or indirect benefit of

dapagliflozin on mortality. This notion was supported by clinical opinion, as indicated in NICE TA902 (152).

To model CV and AC mortality beyond the observed data in DELIVER, a piecewise modelling approach with an inflection point at 1 year was used in NICE TA902. The committee noted that using the Gompertz model to extrapolate both AC and CV mortality increased the ICER, but it considered that the Gompertz model was possibly overly pessimistic. It concluded that there is uncertainty about the method used to incorporate treatment effect on survival, but the initial approach was sufficient for decision making (152).

In NICE TA902, HHF and urgent HHF were modelled by applying generalised estimating equations to DELIVER data. DELIVER data did not clearly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure. The committee concluded that a dapagliflozin treatment effect on urgent HHF should be excluded, but the impact on the ICER was negligible.

Table 8. Clinical outcomes and measures appraised in published NICE STA guidance for the comparator(s)

	Outcome	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
NICE TA902 (Dapagliflozin)	AC mortality	A piecewise modelling approach with an inflection point at 1 year was used to model AC mortality beyond the observed data in DELIVER Scenario analyses using parametric methods was used to extrapolate AC mortality	Committee would have preferred additional scenarios exploring the impact of a direct and/or indirect treatment effect of dapagliflozin on CV and AC mortality which refitted the survival model when parameters were excluded (for example, coefficient for treatment effect and impact of KCCQ state)	The Committee recognised that most plausible scenario would include a dapagliflozin treatment effect on AC and cardiovascular mortality, but uncertainty was still present.
	CV mortality	A piecewise modelling approach with an inflection point at 1 year was used to model CV mortality beyond the observed data in DELIVER Scenario analysis using parametric methods was used to extrapolate CV mortality		
	HHF and urgent hospitalisation for heart failure	Generalised estimating equations were applied to DELIVER data. In the base case, adjusted model (adjusted for patient characteristics and treatment effect) was used	The committee concluded that dapagliflozin treatment effect on urgent hospitalisation for heart failure should be excluded	-
	Utility	EQ-5D-5L data collected in DELIVER was mapped to EQ-5D-3L and used to derive utility values for each KCCQ-TSS quartile	Multiplicative approach rather than an additive approach to derive utility estimates Disutility period for HHF should be 6 months rather than 1 month	-

B.2.2 Resource use assumptions

Cost and resource use data that were considered appropriate in the published NICE TA902 were:

- **Costs of non-elective care, including HHF and inpatient care for AE**: The Committee preferred using NHS reference costs from 2019/2020 and inflating them to 2021 values (instead of incorporating 2020/2021 cost). The Committee considered appropriate to use the weighted average to estimate costs for HHF.

- **Resource use estimate for HHF events**: The unit cost for acute HHF was calculated as the weighted average of reference costs for healthcare resource group (HRG) codes EB03A to EB03E. The EAG's clinical experts considered that the average length of hospital stay for HF was 11 days. The EAG noted that the weighted average approach had included more severe cost codes, for example, EB03A is associated with a 53-day hospital stay. The EAG preferred the scenario using the HRG code EB03E only, which is associated with a 13-day hospital stay, in its preferred base-case. Expert opinion however suggested that only a small number of people with HHF stay in the hospital for 13 days only. The committee acknowledged clinical expert opinion and concluded that it is more appropriate to use the weighted average to estimate costs for HHF.

- **Cost of cardiovascular death**: The Committee considered that the most appropriate costs for cardiovascular death would assume no cost for sudden cardiovascular deaths (£1,452).

- **Annual GP visit**: The Committee considered 6 primary care visits per year (instead of 23.14 GP visits of contacts per year as used in the Company base case) was a reasonable reflection of the monitoring frequency that patients would receive in clinical practice.

B.3 Clinical effectiveness

- Empagliflozin was demonstrated to be efficacious in chronic HF patients across a broad spectrum of EF, (i.e., LVEF ≤40% and LVEF >40% in a combined HF trial analysis) stratified by LVEF (145).
- The results of the EMPEROR-Reduced trial are described in the previous NICE submission TA773 corresponding to an appraisal of empagliflozin for treating chronic HF patients with LVEF ≤40% (5).
- This company submission presents the clinical effectiveness of empagliflozin in the EMPEROR-Preserved trial conducted among patients with LVEF >40%, which completes the evidence package demonstrating the benefits of empagliflozin across a broad spectrum of LVEF for chronic HF patients (4).
- After a median follow-up of 26.2 months, empagliflozin significantly reduced the risk of the primary endpoint, death from CV causes or HHF, compared to placebo (HR, 0.79; 95% CI, 0.69-0.90; p=0.0003).
- Empagliflozin was superior to placebo with respect to key secondary endpoints:
  - It led to a significant reduction in the total number of adjudicated HHF (first and recurrent) (HR, 0.73; 95.03% CI, 0.61 to 0.88; p=0.0009) vs placebo.
  - The rate of the decline in eGFR was slower in empagliflozin group compared to placebo group over the duration of the double-blind treatment period (between-group difference, 1.36 mL/min/1.73 m^2 per year; 95% CI, 1.06 to 1.66; p<0.0001).
- Empagliflozin was also superior to placebo in other secondary endpoints:
  - It reduced risk of adjudicated HHF (first event) (HR, 0.71; 95% CI, 0.60 to 0.83; nominal p<0.0001).
  - It led to improvement in the HRQoL score on KCCQ at 52 weeks (placebo-corrected adjusted mean change from baseline 1.32; 95% CI, 0.45 to 2.19; nominal p=0.0028).
- Empagliflozin was seen to reduce CV mortality (HR, 0.91; 95% CI, 0.76 to 1.09), AC hospitalisation (HR, 0.93; 95% CI, 0.85 to 1.01) and composite renal endpoint (HR, 0.95; 95% CI, 0.73 to 1.24); however, these results were not

statistically significant, nor was the clinical trial sufficiently powered to assess these endpoints.

- The CV and renal benefits of empagliflozin were consistent across subgroups of chronic HF patients (LVEF >40%) defined by demographics, baseline characteristics, and baseline medications.
- In chronic HF patients (LVEF >40%) with diabetes, there was a greater mean reduction in glycated haemoglobin (HbA1c) from baseline in the empagliflozin group than in the placebo group.
- Empagliflozin improves CV and renal outcomes of chronic HF patients (LVEF >40%) including those with an eGFR down to 20 mL/min/1.73 m^2.

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify RCT evidence on the efficacy and safety of empagliflozin and relevant comparators in patients with chronic HF (LVEF >40%, NYHA II-IV). Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are described in Appendix D.

The SLR was conducted according to a pre-agreed protocol and in accordance with the Cochrane Handbook and the Centre for Reviews and Dissemination (CRD). Original searches were performed on 14 May 2020. The first update was performed on 08 October 2020, followed by the second, third, fourth and fifth updates performed on 08 July 2021, 16 February 2022, 07 July 2022 and 23 January 2023, respectively. The results were reported in accordance with the PRISMA reporting checklist.

The eligible studies encompassed all RCTs evaluating efficacy of pharmacological interventions used in the treatment of adults (age ≥18 years) with chronic heart failure with preserved or mildly reduced EF. The search strategy was designed to be broad and to encompass all interventions that are generally used for the management of chronic HF (eligibility criteria are shown in Appendix D). All studies meeting the pre-specified population, intervention, comparator, and outcomes (PICOS) eligibility

criteria were retained and were extracted. A full list of studies that were included and excluded during the SLR is provided in Appendix D.

B.3.1.1 Clinical trials with empagliflozin 10 mg (Jardiance®)

Empagliflozin is being investigated in the EMPOWER clinical trial programme. The most comprehensive development programme for an SGLT2i to date, EMPOWER, is comprised of nine clinical trials and a RWE study that have been designed to evaluate the impact of empagliflozin on CV and renal outcomes of patients across the spectrum of CRM disorders (Table 9). Furthermore, the aim of the programme is to advance the scientific understanding of the pathophysiology of cardio-renal interactions and enable a holistic management of the interconnected CRM organ system.

Table 9. Overview of the studies comprising the EMPOWER clinical trial programme for empagliflozin

Study name	Study identifier	Main objective	Status	Relevant for this appraisal & reason
EMPEROR-Preserved	NCT03057951 (153)	Efficacy & safety of empagliflozin in prevention of CV death and HHF in adults with chronic HF patients (LVEF >40%) with or without T2DM	Completed	Yes, meets the PICO criteria as defined in the decision problem
EMPEROR-Reduced	NCT03057977 (154)	Efficacy & safety of empagliflozin in prevention of CV death and HHF in adults with chronic HFrEF with or without T2DM	Completed	No; population is not relevant for the decision problem
EMPERIAL-Preserved	NCT03448406 (155)	Effect of empagliflozin on functional ability and PROs in adults with chronic HFpEF with or without T2DM	Completed	No; primary outcome is not relevant for the decision problem; QoL secondary endpoint measured using PROs is not recommended by the NICE reference case (121)
EMPERIAL-Reduced	NCT03448419 (156)	Effect of empagliflozin on functional ability and PROs in adults with chronic HFrEF with or without T2DM	Completed	No; population is not relevant for the decision problem

Study name	Study identifier	Main objective	Status	Relevant for this appraisal & reason
EMPA-REG OUTCOME	NCT01131676 (157)	Efficacy & safety of empagliflozin in prevention of major adverse CV events, including CV death, in adults with T2DM and established CV disease	Completed	No; evidence from the trial is not presented separately for patients with HF and LVEF >40%
EMPULSE	NCT04157751 (158)	Efficacy of empagliflozin in improving clinical and PRO outcomes in adults hospitalised for acute HF	Completed	No; population is not relevant for the decision problem
EMPA-KIDNEY	NCT03594110 (159)	Effect of empagliflozin on progression of kidney disease and the occurrence of CV death in patients with pre-existing CKD	Completed	No; population is not relevant for the decision problem
EMPA-VISION	NCT03332212 (160)	Effects on cardiac physiology and metabolism in patients with HF	Completed	No; the study outcomes are not relevant for the decision problem
EMPACT-MI	NCT04509674 (161)	Efficacy of empagliflozin in improving outcomes and preventing HF in adults hospitalised with an acute MI	Ongoing	No; population is not relevant for the decision problem
EMPRISE	NCT03363464 (162) EUPAS20677 (163)	Real-world comparative effectiveness, safety, healthcare resource utilisation and costs of empagliflozin *versus* DPP-4 inhibitors in T2DM in routine clinical care	Ongoing	No; population is not relevant for the decision problem

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalisation for heart failure; MI, myocardial infarction; PICO, patient intervention comparator outcome; PROs, patient-reported outcomes; T2DM, type 2 diabetes mellitus.

Of the studies listed in Table 8, the EMPEROR-Preserved trial provides the main evidence base for clinical efficacy and safety of empagliflozin in the population of HF patients with LVEF >40%. In the trial, randomisation was stratified by LVEF (<50%, ≥50%) and of those enrolled, >66% had LVEF ≥50% (4). It should be noted that the clinical effectiveness of empagliflozin for the treatment of patients with LVEF ≤40% as

studied by the EMPEROR-Reduced trial was appraised by NICE in appraisal TA773 (1, 5).

The EMPEROR-Preserved (NCT03057951) trial was an international phase III trial from the EMPOWER programme that investigated the effect of empagliflozin versus placebo, in addition to usual therapy on the combined risk of CV death and HHF in 5,988 patients with chronic HF (LVEF >40%), with or without diabetes. It also evaluated the effects of empagliflozin on recurrent hospitalisation events, renal function, CV death, all-cause mortality, and change in the Kansas City Cardiomyopathy Questionnaire - clinical summary score (KCCQ-CSS) (153). The EMPEROR-Preserved trial enrolled patients from eight UK sites, increasing its relevance to the NHS clinical practice. External validity of the trial is strengthened by the protocol requirement for patients to receive usual therapy for chronic HF (LVEF >40%).

B.3.1.2 Non-randomised clinical effectiveness studies

Evidence from PULSE, a large retrospective observational study of the burden of chronic HF in England, was used to characterise patients seen in NHS clinical practice. Patients with a diagnosis of HF recorded in the UK CPRD or Hospital Episode Statistics (HES) database between 1 January 2015 and 31 December 2019 were eligible for inclusion in the PULSE study (47). Based on the availability of evidence of EF classification in CPRD records, the cohort was split into EF measure ≤40%, EF measure >40% and “unknown ejection fraction” subpopulations. The study objectives were to determine the incidence and prevalence of HF and associated outcomes, including HF hospitalisation, CV and AC mortality. One of the limitations of using the PULSE study data was that the majority of patients were not coded as per EF subtype at or prior to their HF index date (47). Therefore, other non-randomised clinical effectiveness studies were explored; however, RWE for the population with HF and LVEF >40% are limited. A study by Oo et al. (2021) was considered and the authors conducted a single-centre study to determine clinical characteristics and outcomes of patients defined as preserved EF according to recent guidelines and outcome trials (164). Another study by Uijl et al. (2021) was considered which included patients with LVEF ≥50% and clustered them according to their clinical characteristics (165).

However, these two studies (Oo et al. [2021] and Uijl et al. [2021]) were not considered relevant for this decision problem to appropriately support the evidence package because of missing data and lack of transparency with endpoints (164, 165). Due to lack of available published evidence, and the inappropriateness of the alternative studies considered, the outcomes of the PULSE study are therefore considered the best available evidence to support this decision problem. (47).

B.3.1.3. Clinical trial with dapagliflozin 10 mg (Forxiga)

Dapagliflozin is the only available licenced treatment for chronic HF other than empagliflozin, and it was recently recommended by NICE as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902) on the basis of the DELIVER trial (8, 10). Therefore, dapagliflozin is the only appropriate comparator for empagliflozin for patients with HF and LVEF >40%.

DELIVER was a randomised, double-blind, phase 3 clinical trial, where dapagliflozin plus background therapy for symptom management was compared to placebo plus background therapy for patients with HF and LVEF >40%. DELIVER was found to have comparable study design to the EMPEROR-Preserved trial (see section B.3.9 and Appendix D).

B.3.2 List of relevant clinical effectiveness evidence

The clinical evidence for empagliflozin as an addition to background therapy for symptom management (i.e., treatments used to treat CV comorbidities) in the treatment of chronic HF (LVEF >40%) consists of one phase III trial, EMPEROR-Preserved (Table 10).

Table 10. Clinical effectiveness evidence: EMPEROR-Preserved trial

Study	EMPEROR-Preserved (NCT03057951) (153)
Primary sources	Anker et al 2021 (4)
Additional sources	EMPEROR-Preserved CSR (166)
Study design	• Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment

Study	EMPEROR-Preserved (NCT03057951) (153)
	• The trial was event-driven, and all randomised patients remained in the trial until the defined number of adjudicated primary endpoint events had been reached
Population	Adults with chronic HF NYHA class II-IV and LVEF >40% who have been diagnosed at least 3 months before screening, with or without DM • N=5,988 • Age ≥18 years • Baseline natriuretic peptide levels >300 pg/mL for patients without atrial fibrillation or atrial flutter (AF); >900 pg/mL for patients with AF at screening (see Section 0) • Oral diuretics, if prescribed to patient according to local guidelines and discretion of the investigator, should have been stable for at least 1 week prior to (randomisation)
Intervention(s)	Empagliflozin PO 10 mg once daily in addition to background therapy for symptom management (i.e., treatments used to treat CV comorbidities)
Comparator(s)	Placebo plus background therapy for symptom management
Does trial support application for MA?	Yes
Reported outcomes specified in the decision problem	The outcomes relevant for the decision problem include: • Time to first event of adjudicated CV death or adjudicated HHF • Occurrence of adjudicated HHF (first and recurrent) • Decline in renal function • Time to first occurrence of chronic dialysis, renal transplant or sustained reduction of eGFR • Time to first adjudicated HHF • Time to adjudicated CV death • Time to AC mortality • Occurrence of AC hospitalisation • Adverse effects of treatment • PRO measured by KCCQ • HRQoL measured by EQ-5D-5L
All other reported outcomes	• Other clinical outcome events o 3-point MACE (adjudicated CV death, adjudicated non-fatal MI, or adjudicated non-fatal stroke) o Adjudicated MI (fatal or non-fatal) o Composite of adjudicated CV death or adjudicated non-fatal MI

Study	EMPEROR-Preserved (NCT03057951) (153)
	○ 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 • NYHA class change from baseline • Body weight change from baseline • Blood pressure change from baseline • Pulse rate change from baseline • NT-proBNP change from baseline • eGFR change from baseline • Albuminuria • Health economic analysis by HCRU

Abbreviations: CSR: Clinical study report; CV: Cardiovascular; EQ-5D: EuroQoL 5-Dimensiosn; HCRU: Healthcare resource utilisation; HF: Heart failure; HHF: Hospitalisation for heart failure; MACE: Major adverse cardiovascular events: MI: Myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PRO: Patient reported outcome;

The clinical effectiveness evidence comparing the EMPEROR-Preserved versus DELIVER clinical trials for empagliflozin and dapagliflozin, respectively are presented in Appendix D.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Summary of methodology of the EMPEROR-Preserved trial (NCT03057951)

EMPEROR-Preserved was an international phase III study designed to evaluate the long-term efficacy and safety of empagliflozin versus placebo in addition to guideline-directed medical therapy in patients with symptomatic chronic HF (LVEF >40%) (4). The trial had a double-blind, placebo-controlled, randomised design with parallel assignment of participants in 1:1 ratio to one of the two treatment arms:

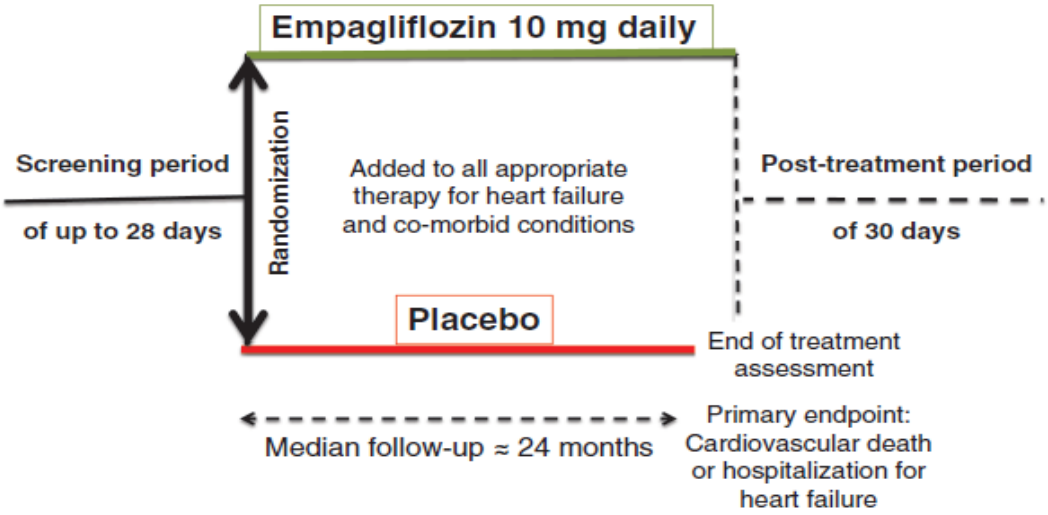
- Empagliflozin, 10 mg PO once daily in addition to background therapy (usual therapy i.e., treatments used to treat CV comorbidities which could include

treatment with a low to medium dose of loop diuretic, ACEI, ARB, mineralocorticoid receptor antagonist, beta-blocker and/or sacubitril/valsartan), or

- Placebo PO once daily in addition to the background therapy for symptom management.

Following a screening period lasting 4–28 days, patients who fulfilled all eligibility criteria were randomised to receive placebo or empagliflozin daily in addition to their usual therapy for HF. The EMPEROR-Preserved trial design is illustrated in Figure 6 (146).

Figure 6: Design of EMPEROR-Preserved trial



Source: Adapted from Anker et al, 2019 (146).

Randomisation was performed using a permuted block design with a computer pseudo-random number generator and was stratified by:

- geographical region (North America, Latin America, Europe, Asia or “Other”),
- history of diabetes (diabetes, pre-diabetes and no diabetes),
- eGFR (by the Chronic Kidney Disease - Epidemiology Collaboration Equation [CKD-EPI] equation) at screening <60 or ≥60 mL/min/1.73 m², and
- LVEF (<50%, ≥50%).

Following randomisation, all appropriate treatments for HF or other medical conditions were initiated and individualised at the discretion of each subject’s physician. Patients were evaluated periodically at pre-specified study visits.

The primary objective of the EMPEROR-Preserved was to compare the time to first event of adjudicated CV death or adjudicated HHF among patients taking empagliflozin relative to those taking placebo in addition to their standard CRM therapy. The trial also evaluated the effects of empagliflozin on recurrent HHF, renal function, CV death, all-cause mortality, and quality of life.

EMPEROR-Preserved was an event-driven trial and all randomised patients remained in the study until the defined number of adjudicated primary endpoint events were reached. As such, EMPEROR-Preserved was appropriately designed to determine if the addition of empagliflozin can improve outcomes of chronic HF (LVEF >40%) since the current treatment options show limited benefit for patients with chronic HF and a preserved EF. Aspects of the trial methodology are described in more detail below in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (167).

B.3.3.1.1 Changes to trial design

The description of the EMPEROR-Preserved methodology outlined in this submission is based on the revised study protocol number c03946327-04 which was issued on 20 November 2019 and incorporates Global Amendment 03.

B.3.3.1.2 Eligibility criteria for study participants

The intent of the EMPEROR-Preserved trial was to recruit chronic HF (LVEF >40%) patients on various HF background therapies to evaluate the long-term effect of empagliflozin on CV death and HHF in a real-life clinical setting. The trial, therefore, included adult patients with chronic HF with LVEF >40% diagnosed at least 3 months before screening and in the functional NYHA class II-IV. Details of inclusion and exclusion criteria are presented in Table 11.

Table 11. Inclusion and exclusion criteria of the EMPEROR-Preserved trial

Inclusion criteria	• Males and females aged ≥18 years; for Japan only: age ≥20 years • Patients with chronic HF diagnosed for at least 3 months before screening, and currently in HF NYHA class II-IV • Chronic HF with preserved EF defined as LVEF >40% per local reading

	• In addition to LVEF >40%, patient must have NT-proBNP >300 pg/mL for patients without AF, or >900 pg/mL for patients with AF (analysed at the Central Laboratory at screening) • Patients with either documented structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) within 6 months or HHF documented within 12 months prior to screening • Oral diuretics, if prescribed to patients according to local guidelines and discretion of the investigator, must be stable for at least one week prior to randomisation • BMI <45 kg/m^2 at screening
Exclusion criteria	• MI (increase in cardiac enzymes in combination with symptoms of ischaemia or new ischaemic ECG changes), CABG or other major CV surgery, stroke or transient ischaemic attack in past 90 days • Heart transplant recipient or listed for heart transplant • Cardiomyopathy based on infiltrative diseases (amyloidosis), accumulation diseases (haemochromatosis, 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 HF requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomisation • Implanted cardioverter defibrillator within 3 months prior to screening • Cardiac resynchronization therapy • Atrial fibrillation or AF with a resting heart rate >110 bpm, documented by ECG at screening • SBP ≥180 mmHg at randomisation. If SBP is 151–179 mmHg, the patient should be receiving ≥3 anti-hypertensive drugs • Symptomatic hypotension and/or a SBP <100mmHg at screening or at randomisation • Chronic PD requiring home oxygen, oral corticosteroid therapy or hospitalisation for exacerbation within 12 months, significant chronic PD or primary pulmonary arterial hypertension • Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3x ULN as determined at randomisation • Impaired renal function, defined as eGFR <20 mL/min/1.73 m^2 (CKD-EPI) or requiring dialysis at the time of screening • Haemoglobin <9 g/dL at screening • History of ketoacidosis • Major surgery performed within 90 days prior to screening or major scheduled elective surgery (e.g., hip replacement) within 90 days after screening • GI surgery or GI disorder that could interfere with 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 • Presence of any other disease with a life expectancy of <1 year in the opinion of the investigator) • Current use or prior use of a SGLT2i or combined inhibitor of SGLT1 and SGLT2 within 12 weeks prior to screening or randomisation • Currently enrolled in another investigational device or drug study or are less than 30 days since the completion of a trial of another investigational device or drug. Any patient receiving any investigational treatment other than the study medications for this trial • Known allergy or hypersensitivity to any SGLT2i • Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial • Women who are pregnant or are nursing or who plan to become pregnant while in the trial • Any other clinical condition that would jeopardise patient safety while participating in this trial or may prevent the subject from adhering to the trial protocol

Abbreviations: AF, atrial fibrillation or atrial flutter; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; bpm, beats per minute; CABG, coronary artery bypass grafting; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CV, cardiovascular; ECG electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; ICD, implantable cardioverter-defibrillator; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PD, pulmonary disease; SGLT, sodium-glucose co-transporter; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal.

Appendix D, Table 18 presents the detailed inclusion and exclusion criteria of the EMPEROR-Preserved and DELIVER clinical trials for empagliflozin and dapagliflozin, respectively.

B.3.3.1.3 Study locations

Patient enrolment (N=5,988) started on 27 March 2017 in university hospitals, specialist CV clinics and clinical research centres across 622 locations in 23 countries (Poland, Czech Republic, Hungary, Germany, the Netherlands, Italy, Romania, Spain, Belgium, UK, Brazil, Argentina, Colombia, Mexico, US, Canada, Japan, China, Korea, Singapore, South Africa, Australia and India). From the UK, 53 patients were enrolled of which 25 patients were randomised and treated. The study completion date was 26 April 2021.

B.3.3.1.4 Trial drugs and concomitant medications

Study interventions are summarised in Table 12. The use of medication for the treatment of HF was at the discretion of the investigator and was to be in accordance with local and international guidelines. Disallowed concomitant medications included any SGLT2i or combined SGLT1 and 2 inhibitors, except the blinded trial medication.

Table 12. EMPEROR-Preserved trial drugs

Drug	Dose	Frequency of administration	Route of administration	Duration
Empagliflozin, film coated tablet	10 mg	Once daily	Oral	Until the necessary number of events were observed to evaluate efficacy for the primary composite endpoint
Placebo matching empagliflozin, film coated tablet	-			

B.3.3.1.5 Pre-specified primary and secondary outcomes of EMPEROR-Preserved

The endpoints relevant for the decision problem are summarised in Table 13. The definitions of adjudicated CV endpoints are summarised in Table 14.

Table 13. Pre-specified primary and secondary outcomes

Primary endpoint	Definition	NICE scope
Combined risk of CV death or HHF	A composite of adjudicated CV death or HHF, analysed as the time to the first event	Per NICE scope
Key secondary endpoints	**Definition**	**NICE scope**
Total HHF (first and recurrent)	Occurrence of adjudicated HHF (first and recurrent)	Per NICE scope
Rate of renal function decline	eGFR (CKD-EPI)cr slope of change from baseline	Per NICE scope
Other secondary endpoints	**Definition**	**NICE scope**
Risk of composite renal endpoint (chronic dialysis,	Time to first event in the composite renal endpoint: occurrence of chronic dialysis[a] or renal transplant or sustained[b] reduction in eGFR (CKD-EPI)cr[c]	Per NICE scope

renal transplant or renal insufficiency)		
Risk of first HHF	Time to first adjudicated HHF	Per NICE scope
Risk of CV death	Time to adjudicated CV death	Per NICE scope
Risk of death	Time to AC mortality	Per NICE scope
Risk of diabetes mellitus	Time to onset of 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%)	Not in scope
Change in KCCQ clinical summary score	Change from baseline in the KCCQ clinical summary score (HF symptoms and physical limitations domains) at week 52	Per NICE scope
Risk of AC hospitalisation	Occurrence of AC hospitalisation (first and recurrent)	Per NICE scope
Further endpoints	**Definition**	**NICE scope**
Risk of atrial fibrillation	New onset of atrial fibrillation	Not in scope
Risk of myocardial infarction	Adjudicated MI (fatal or non-fatal)	Not in scope
Risk of stroke	Adjudicated stroke (fatal or non-fatal)	Not in scope
Safety	AE, AE of special interest and specific adverse events	Per NICE scope

Abbreviations: CV, cardiovascular; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HF, heart failure; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire.

[a]Chronic dialysis was defined as dialysis with a frequency of twice per week or more for at least 90 days

[b]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)

[c]Reduction in eGFR (CKD-EPI)cr was defined as reduction in eGFR from baseline of ≥40%, eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2, or eGFR <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2

The pre-specified primary and secondary outcomes of EMPEROR-Preserved and DELIVER clinical trials for empagliflozin and dapagliflozin are presented in Table 22 of Appendix D.

Table 14. Definitions of adjudicated endpoints

Endpoint	Definition[a]
HHF	HHF endpoint must meet the following criteria: • Adjudicated primary diagnosis is admission to hospital for HF

Endpoint	Definition[a]
	• Length of stay in hospital extends for ≥12 hours (emergency room visit for ≥12 hours with IV therapy is considered equivalent to admission to hospital) • The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following: o Dyspnoea (dyspnoea with exertion, dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea) o Decreased exercise tolerance o Fatigue o Other symptoms of worsened end-organ perfusion (dizziness, confusion, or volume overload such as weight gain or lower extremity swelling) • Objective evidence of new or worsening HF consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion, including: o Physical examination findings considered to be due to HF: - Peripheral oedema - Increasing abdominal distension or ascites - Pulmonary rales/crackles/crepitations - Increased jugular venous pressure and/or hepatojugular reflux - S3 gallop - Clinically significant rapid weight gain related to fluid retention o Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: - Increased BNP/NT pro-BNP concentrations consistent with decompensation of HF - Radiological evidence of pulmonary congestion - Non-invasive evidence of clinically significant left- or right- sided ventricular filling pressure or low cardiac output, *or* - Invasive diagnostic evidence with right heart catheterisation showing a pulmonary capillary wedge pressure ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/L[2] • The patient receives initiation or intensification of treatment for HF, including at least one of the following: o Augmentation in oral diuretic therapy o IV diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator) o Mechanical or surgical intervention (circulatory support with intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart or fluid removal with ultrafiltration, hemofiltration, dialysis)
CV death	CV death includes the following categories:

Endpoint	Definition[a]
	• Death due to MI, a procedure to treat MI or elective coronary procedure to treat myocardial ischaemia • Death due to clinically worsening signs and symptoms of HF including cardiogenic shock and pulmonary oedema • Death due to stroke, CV procedures, CV haemorrhage or other CV causes (e.g., pulmonary embolism or peripheral arterial disease) • Sudden cardiac death, including: o Death witnessed and occurring without new or worsening symptoms o Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms o Death witnessed and attributed to an identified arrhythmia or unwitnessed but found on implantable cardioverter-defibrillator review o Death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest without identification of a specific cardiac or non-cardiac aetiology o Unwitnessed death in a subject seen alive and clinically stable ≤ 72 hours prior to being found dead without any evidence supporting a specific non-CV cause of death

Abbreviations: CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure; BNP, B-type natriuretic peptide; NT pro-BNP, N-terminal pro-B- type natriuretic peptide; MI, myocardial infarction.
[a]All CV endpoint definitions were modifications of the guideline recommendations by Hicks et al 2014 (168).

Table 23 of Appendix D provides a comparison of definitions of adjudicated endpoints of EMPEROR-Preserved and DELIVER clinical trials for empagliflozin and dapagliflozin.

B.3.3.2 Summary of trial methodology

The summary of pivotal EMPEROR-Preserved trial is described in **Table *15***. A comparative summary of the EMPEROR-Preserved and DELIVER clinical trials for empagliflozin and dapagliflozin is presented in Table 21 of Appendix D.

Table 15. Summary of trial methodology for EMPEROR-Preserved trial

Study	EMPEROR-Preserved (4)
Trial number	• NCT03057951
Trial design	• Phase III, randomised, double-blind, placebo-controlled trial with parallel assignment • The trial was event-driven and all randomised patients remained in the trial until the defined number of adjudicated primary endpoint events had been reached
Eligibility criteria for participants	• Males and females aged ≥18 years; for Japan only: age ≥20 years

Study	EMPEROR-Preserved (4)
	• Patients with chronic HF diagnosed for at least 3 months before screening, and currently in HF NYHA class II-IV • Chronic HF with preserved EF defined as LVEF >40% per local reading • In addition to LVEF >40%, patient must have NT-proBNP >300 pg/mL for patients without AF, or >900 pg/mL for patients with AF (analysed at the Central Laboratory at screening) • Patients with either documented structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) within 6 months or HHF documented within 12 months prior to screening • Oral diuretics, if prescribed to patients according to local guidelines and discretion of the investigator, must be stable for at least one week prior to randomisation • BMI <45 kg/m^2 at screening
Settings and locations where the data were collected	• Patient enrolment (N=5,988) started on 27 March 2017 in university hospitals, specialist CV clinics and clinical research centres across 622 locations in 23 countries (Poland, Czech Republic, Hungary, Germany, the Netherlands, Italy, Romania, Spain, Belgium, UK, Brazil, Argentina, Colombia, Mexico, US, Canada, Japan, China, Korea, Singapore, South Africa, Australia and India). From the UK, 53 patients were enrolled of which 25 patients were randomised and treated. The study completion date was 26 April 2021.
Intervention and competitors **Permitted and disallowed concomitant medication**	• Intervention: Empagliflozin PO 10 mg once daily in addition to background therapy (usual therapy i.e., treatments used to treat CV comorbidities) (n=2997) • Competitor: Placebo plus background therapy for symptom management (n=2991) • Concomitant medication: Disallowed concomitant medications included any SGLT2i or combined SGLT1 and 2 inhibitors, except the blinded trial medication.
Primary outcomes	• Combined risk of CV death or HHF (A composite of adjudicated CV death or HHF, analysed as the time to the first event)
Pre-planned subgroups	• Diabetes at baseline (diabetic, non-diabetic patients) • Renal function at baseline (eGFR ≥60 mL/min/1.73 m^2, <60 mL/min/1.73 m^2) • Gender • Race (White, Black, Asian, other) • BMI (<30 kg/m^2 and ≥30 kg/m^2) • Age (<70 years and ≥70 years) • SBP at baseline • History of AF • HHF in the last 12 months • NYHA at baseline (II, III/IV)

Study	EMPEROR-Preserved (4)
	• Uric acid, in thirds, at baseline • HF physiology (reflected in baseline LVEF and level of NT-pro-BNP) • Baseline use of mineralocorticoid receptor antagonist • Baseline use of ACEI, ARB, or ARNI at baseline • Geographic region (Asia, Europe, Latin America, North America, and other)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

B.3.3.3 Demographics and baseline characteristics

Patients in the empagliflozin and the placebo group were well balanced with respect to demographic and clinical characteristics at baseline (Table 16). About a third of patients were in each of the pre-defined LVEF categories (LVEF <50%, 50 to <60%, and ≥60%). An eGFR of <60 mL per minute per 1.73 m^2, a history of AF or flutter and T2DM were reported for around 50% of the patients. A majority of patients were in HF NYHA class II (81.5%) while a third of patients had HF diagnosis for at least 5 years before the trial.

Table 16. Demographic and baseline characteristics of randomised participants in EMPEROR-Preserved trial

EMPEROR-Preserved (NCT03057951) Baseline characteristic[a]	Empagliflozin 10 mg	Placebo
Number of subjects	2,997	2,991
Age (years), mean (SD)	71.8 (9.3)	71.9 (9.6)
Female sex, N (%)	1,338 (44.6)	1,338 (44.7)
Race, N (%)[b]		
White	2,286 (76.3)	2,256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other including mixed race	165 (5.5)	199 (6.7
Region, N (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1,346 (44.9)	1,343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional class, N (%)		
I	3 (0.1)	1 (<0.1)
II	2,432 (81.1)	2,451 (81.9)
III	552 (18.4)	531 (17.8)
IV	10 (0.3)	8 (0.3)

BMI[c] (kg/m^2), mean	29.8+/-5.8	29.9+/-5.9
Heart rate (beats/min), mean	70.4+/-12.0	70.3+/-11.8
SBP (mm Hg), mean	131.8+/-15.6	131.9+/-15.7
DBP (mm Hg), mean	75.7+/-10.6	75.7+/-10.5
LVEF		
Mean	54.3+/-8.8	54.3+/-8.8
Value of <50%, N (%)	995 (33.2)	988 (33.0)
Value of 50% to >60, N (%)	1,028 (34.3)	1,030 (34.4)
Value of ≥60%, N (%)	974 (32.5)	973 (32.5)
NT-proBNP (pg/mL)		
Median (IQR)	994 (501-1740)	946 (498-1725)
Time since diagnosis of HF (years)		
Mean	4.5+/-5.2	4.3+/-5.0
≤1 year, N (%)	730 (24.4)	782 (26.1)
>1 to 5 years, N (%)	1,368 (45.6)	1,325 (44.3)
>5 to 10 years, N (%)	550 (18.4)	553 (18.5)
>10 years, N (%)	349 (11.6)	331 (11.1)
Cause of HF, N (%)		
Ischaemic	1,079 (36.0)	1,038 (34.7)
Nonischaemic	1,917 (63.9)	1,953 (65.3)
CV history, N (%)		
Hospitalisation for HF in ≤12 months	699 (23.3)	670 (22.4)
Atrial fibrillation	1,543 (51.5)	1,514 (50.6)
Hypertension	2,721 (90.8)	2,703 (90.4)
Estimated glomerular filtration rate		

Mean (mL/min/1.73 m²)	60.6+/-19.8	60.6+/-19.9
Value of <60 mL/min/1.73 m², No (%)	1,504 (50.2)	1,484 (49.6)
UACR (mg/mL)		
Normal (<30), N (%)	1,727 (57.6)	1,747 (58.4)
Microalbuminuria (30 to ≤300), N (%)	939 (31.3)	921 (30.8)
Macroalbuminuria (>300), N (%)	318 (10.6)	311 (10.4)
HF medication, N (%)		
ACEI/ARB/ARNI	2,428 (81.0)	2,404 (80.4)
ARNI	65 (2.2)	69 (2.3)
Beta-blocker	2,598 (86.7)	2,569 (85.9)
Diuretics	2,563 (85.5)	2,600 (86.9)
Lipid-lowering drugs	2,103 (70.2)	2,139 (71.5)
Anti-thrombotic drugs	2,631 (87.8)	2,609 (87.2)
Diabetes status		
Without diabetes, N (%)	1,531 (51.1)	1,519 (50.8)
Without diabetes or pre-diabetes, N (%)	530 (17.7)	540 (18.1)
With pre-diabetes, N (%)	1,001 (33.4)	979 (32.7)
With diabetes, N (%)	1,466 (48.9)	1,472 (49.2)
T2DM, N (%)	1,461 (48.7)	1,467 (49.0)
T1DM, N (%)	5 (0.2)	5 (0.2)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; DBP, diastolic blood pressure; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; No, number; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; T1DM, type 1 DM; T2DM, type 2 DM; UACR, urine albumin-to-creatinine ratio.
Notes: Patients with information missing are not shown.
[a]Plus-minus values are means ± SD. Percentages may not total 100 because of rounding.
[b]Race was reported by the patients. Those who identified with more than one race or with no race were classified as "other".
[c]The BMI is the weight in kilograms divided by the square of the height in metres.
Source: EMPEROR-Preserved CSR Table 10.4.1: 1, 10.4.2: 1, 10.4.3: 1; Table 10.4.4.1 (166).

A comparison of demographic and baseline characteristics of randomised participants in the EMPEROR-Preserved and DELIVER trials of empagliflozin and dapagliflozin is presented in Table 24 of Appendix D.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical analysis methods and definitions of study groups used in the pivotal EMPEROR-Preserved trial are described in Table 17. The methods of statistical analysis were similar to the EMPEROR-Reduced trial, which has been assessed in the TA773 appraisal (1).

B.3.4.1 Statistical methods and analysis sets

Table 17. Summary of statistical analysis in the EMPEROR-Preserved

Study name (number)	EMPEROR-Preserved (NCT03057951)
Research hypothesis	There is no difference between the efficacy of empagliflozin and efficacy of placebo in reducing the combined risk of CV death and HHF.

Analysis sets	• **Randomised set:** All randomised patients, whether treated or not
	  ○ OC-AD: Observed case including data after treatment discontinuation
	  ○ OC-OT: Observed case on-treatment
	• **Treated set:** All patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
	• **Treated Set-Follow-up (TS-FU):** All patients in the TS who performed the follow-up visit. Patients who took open-label SGLT-2 inhibitor between their end of treatment and follow-up visit were excluded from TS-FU.
	• **Pharmacokinetic set (PKS):** All patients in the TS who provided at least one observation for any empagliflozin PK parameter.

Statistical analysis for primary endpoint	The primary and key secondary endpoints were tested in the following hierarchical order: • Time to first event of adjudicated CV death or adjudicated HHF • Occurrence of adjudicated HHF (first and recurrent) • eGFR (CKD-EPI)cr slope of change from baseline For each of these confirmatory endpoints, superiority of empagliflozin over placebo was evaluated with a two-sided test. The overall type I error rate for the trial was preserved at α = 0.05. Due to the amount of α spent on the interim analysis, the remaining two-sided α level for the final analysis was 0.0497. The primary analysis was a Cox PH regression with factors treatment, geographical region, diabetes status at baseline, age, gender, LVEF, and baseline eGFR (CKD-EPI)cr. Following the ITT principle, the primary analysis was based on RS using all data up to the end of the planned treatment period (including the data after end of treatment for patients not completing the treatment phase as

Study name (number)	EMPEROR-Preserved (NCT03057951)
	planned). Patients without a specific endpoint event were censored at the last date the patient was known to be event free or at the end of the planned treatment period, whichever was earlier. When violation of the PH assumption was observed, groups of patients for which the proportionality assumption held were identified, and a stratified Cox regression was performed.
Statistical analysis for key secondary endpoints	• **Occurrence of adjudicated HHF (first and recurrent)** was analysed by a joint frailty model that accounted for the dependence between recurrent HHF and CV death. The primary analysis included all data until completion of the planned treatment phase, including the data after end of treatment for patients not completing the treatment phase as planned. The model included the same covariates used for the analysis of the primary endpoint. The evaluation was assigned an alpha level of 0.0497. The joint model provided two distinct HRs: o HR_{HHF} associated with the effect of treatment on the recurrent event rate of HHF o HR_{CVD}, the HR for CV death. • **Slope in change from baseline of eGFR (CKD-EPI)cr** was analysed by a random coefficient model allowing for random intercept and random slope per patient, with the same factors used for the primary endpoint and the additional factors time, treatment-by-time and baseline eGFR (CKD-EPI)cr-by-time interaction as linear covariates. The model included all on-treatment change from baseline. This endpoint was tested with a two-sided α of 0.001.
Statistical analysis of exploratory endpoints	• **Time to event endpoints:** as analysis of primary endpoint • **Recurrent event endpoints:** as analysis of the first key secondary endpoint • **Continuous endpoints:** mixed model repeated measure (MMRM) analysis • **Categorial endpoints:** descriptive
Sample size & power calculation	Sample size calculation was based on the number of events needed to achieve power of 90% for a two-sided test with α=0.05 and HR 0.80. Achieving that treatment effect size required 841 primary endpoint events. Assuming a 10% event rate per year in the placebo arm, a recruitment period of 18 months and a follow-up period of 20 months, 4,126 patients needed to be randomised to receive empagliflozin or placebo in 1:1 manner.
Data management, patient withdrawals	• **Handling of drop-outs or missing data:** o For patients without primary event and lost to follow-up before trial completion, the treatment specific incidence rates for empagliflozin and placebo for retrieved drop-outs were used to impute the primary events in a multiple imputations framework. The primary model was applied to the imputed datasets. o There was no imputation of data for safety analyses or for time to event endpoints. o For endpoints of KCCQ scores in case of patients who die, a score of 0 was imputed at all subsequent scheduled visits where the score would have been assessed. o Missing covariates in multivariate Cox regression models and for recurrent event analyses were imputed using the overall population median of the corresponding variable for continuous covariates and the most frequent category for categorical covariates. No imputation was done for covariates included in treatment by subgroup interaction terms.

Study name (number)	EMPEROR-Preserved (NCT03057951)
	• **Subjects could have been instructed to permanently discontinue study drug only after discussion with investigator if:** ○ eligibility criteria were violated ○ in the case of an AE ○ if the patient failed to comply with the protocol if any restricted treatment was given during the trial

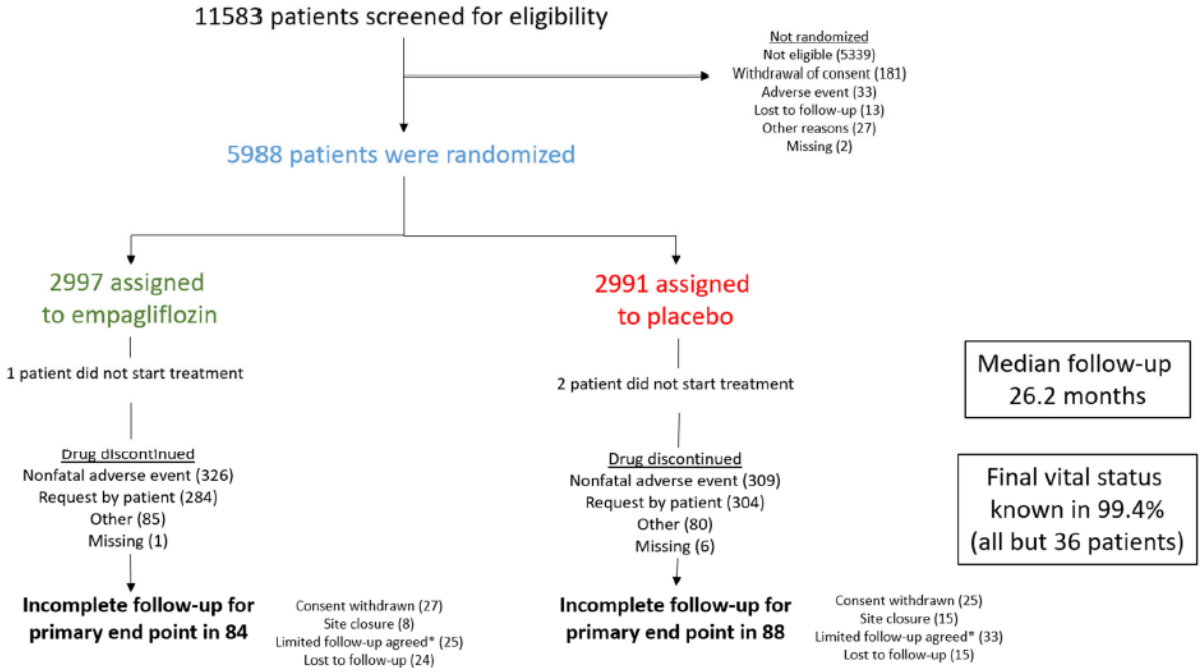
Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular death; (CKD-EPI)cr, Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine measurement; CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; EF, ejection fraction; EOT, end of treatment; EQ-5D, EuroQol 5 dimensions instrument; FU, follow-up; HES, Hospital Episode Statistics; HF, heart failure; HHF, hospitalisation for heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; eGFR, estimated glomerular filtration rate; ITT, intention to treat; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MMRM, mixed model repeated measure analysis; PH, proportional hazards; RS, randomised set; SCR, screened set; SGLT2, sodium-glucose co-transporter 2;; TS, treated set; TS-FU, treated set with follow-up.
Source: Anker et al 2021 (4); EMPEROR-Preserved CSR (166).

Table 25 in Appendix D presents the summary of statistical analysis in the EMPEROR-Preserved and DELIVER trials for empagliflozin and dapagliflozin, respectively.

B.3.4.2 Participant flow in the relevant randomised controlled trials

Participant flow in EMPEROR-Preserved is shown in Figure 7.

Figure 7. CONSORT diagram of patient flow in each stage of the EMPEROR-Preserved RCT



Notes: Incomplete follow-up for the primary end point refers to incomplete information on either vital status or hospitalisation until the planned end of the treatment period for those patients who had not experienced an adjudicated primary outcome. The 36 patients with unknown vital status at the end of the trial included 17 on empagliflozin and 19 on placebo. Five patients with missing vital status at the end of the trial experienced an adjudicated HHF and are not considered to have incomplete follow-up for the

primary endpoint. Asterisk denotes patients who discontinued study medication before the trial end but agreed to collection of vital status data at trial completion.
Source: Anker et al 2021 (4).

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment of EMPEROR-Preserved, a parallel-group RCT, is shown in Table 18. The complete quality assessment is provided in Appendix D. The quality appraisal was similar to the EMPEROR-Reduced trial, which has been assessed in the TA773 appraisal (1).

Table 18. Results of the quality assessment of the EMPEROR-Preserved trial

Quality assessment questions	EMPEROR-Preserved (NCT03057951)
Was randomisation carried out appropriately?	Yes. Randomisation was performed by using a permuted block design with a computer pseudo-random number generator.
Was the concealment of treatment allocation adequate?	Yes. An Interactive Response Technology System (voice response or web response) was used to determine treatment assignment.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and patient characteristics were well balanced between the two treatment groups at baseline, and randomisation was stratified by geographical region, diabetes status and eGFR at screening.
Were the care providers, participants and outcome assessors blind to the treatment allocation?	Yes. This was a double-blind study. Independent external clinical event committees evaluated all reported and potential clinical events in a manner blinded to the treatment assignment.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Proportion of patients who discontinued study treatment was low and well balanced between the two treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes specified in the study protocol were reported in the clinical study report.
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed in the randomised set.

A quality assessment comparison of EMPEROR-Preserved and DELIVER clinical trials of empagliflozin and dapagliflozin is presented in Table 26 of Appendix D.

B.3.6 Clinical effectiveness results of the relevant studies

As described in sections that follow, the null hypotheses for the primary and the two key secondary endpoints of the EMPEROR-Preserved trial were rejected in a hierarchical testing procedure. Results of the trial demonstrate that empagliflozin is superior to placebo in improving HF outcomes in patients with symptomatically stable chronic HF (LVEF >40%). Empagliflozin treatment demonstrated a clinically meaningful and statistically significant reduction in the risk of CV death or HHF (primary endpoint), compared with placebo. The benefit was consistent across pre-specified LVEF subgroups and irrespective of diabetes status at baseline. In comparison to placebo, addition of empagliflozin to background therapy is also associated with a slower decline of renal function as assessed by eGFR slope of change (4). It should be noted that the primary and secondary outcomes (except time to composite renal outcome) of the EMPEROR-Preserved trial were similar to the EMPEROR-Reduced trial which has been assessed in the NICE appraisal TA773 (1).

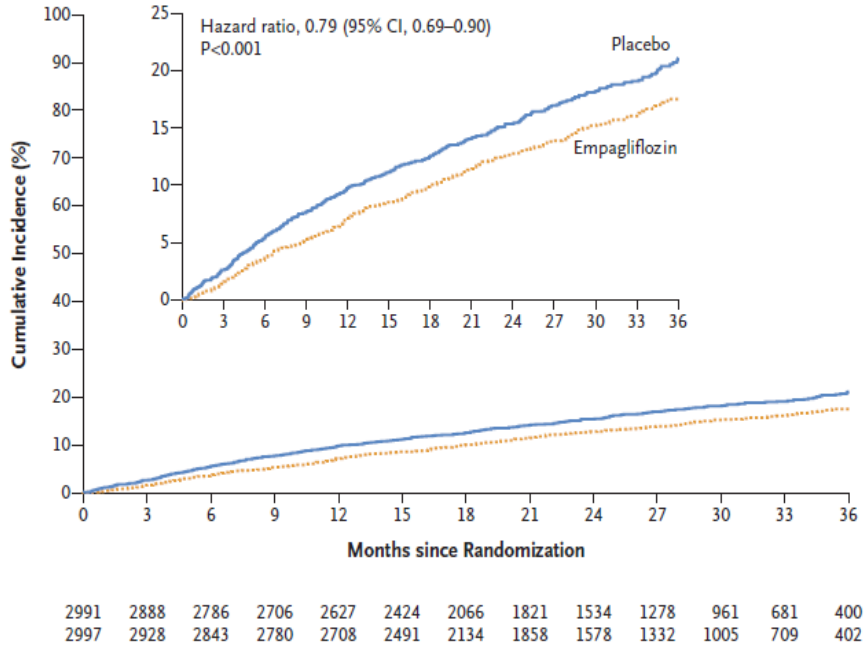
Results of the pre-specified efficacy outcomes that are within the scope of the decision problem are described in Sections B.3.6.1 Primary outcome: combined risk of CV death or HHF to B.3.6.2 Secondary outcomes. The results of a combined HF analysis stratified by LVEF are also described in Section B.3.6.3 Effect of empagliflozin in patients with HF across spectrum of LVEF. Pre-specified subgroup analysis of the trial data relevant to the decision problem is described in Appendix E.

B.3.6.1 Primary outcome: combined risk of CV death or HHF

The primary composite outcome of CV death or HHF occurred in a lower proportion of patients in the empagliflozin group (415 of 2,997 patients, 13.8%) than in the placebo group (511 of 2,991 patients, 17.1%). The separation of the estimated cumulative incidence of CV death or first HHF curves, considering non-CV death as a competing risk, started shortly after randomisation and was maintained throughout the trial period (Figure 8). Cox regression of data for all randomised patients adjusted for age, baseline eGFR (CKD-EPI)cr, region, gender, treatment, baseline diabetes status and

LVEF, revealed that the risk of CV death or HHF was significantly reduced with empagliflozin compared with placebo (HR, 0.79; 95% CI, 0.69 to 0.90).

Figure 8. Primary outcome, a composite of CV death or HHF



Abbreviation: CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.
Source: Figure 1, Anker et al 2021 (4).

During a median trial period of 26 months, the number of patients treated with empagliflozin needed to prevent one primary outcome event was 31 (95% CI, 20 to 69).

Several sensitivity analyses of the primary endpoint were performed to consider competing risks and to account for missing follow-up data in 172 patients who discontinued trial prematurely. The results of sensitivity analysis were generally consistent with the results of the primary analysis, with similar HRs (Table 19).

Table 19. Sensitivity analyses for the primary endpoint: time to the first event of adjudicated CV death or HHF

Sensitivity analyses in RS	HR (95% CI)
Multiple imputation analysis addressing incomplete data for primary endpoint[a], RS	0.79 (0.70-0.90)
Results unadjusted for covariates, RS	0.79 (0.70-0.90)
Sub-distribution HR adjusted for non-CV death as a competing risk in RS (Fine-Gray model)[b]	0.78 (0.69-0.89)

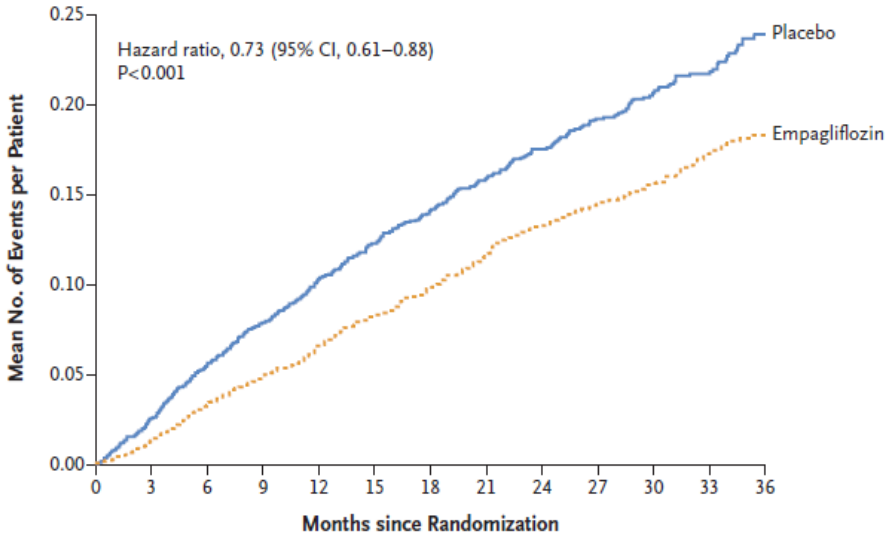
Abbreviations: CV, cardiovascular; HHF, hospitalisation for heart failure; RS, randomised set.
[a]Imputations were performed for 172 patients with incomplete data (84 empagliflozin, 88 placebo). Treatment specific incidence rates for empagliflozin and placebo for patients who discontinued study medication with available follow-up data were used to impute the primary events in a multiple imputations framework via sampling from an exponential distribution. One hundred imputations were performed and evaluated by the primary model. Log hazard ratios were summarised by Rubin's rules (169).
[b]Fine and Gray, 1999 (170).
Source: EMPEROR-Preserved CSR, Figure 11.1.1.2: 1 (166).

B.3.6.2 Secondary outcomes

B.3.6.2.1 Total HHF (first and recurrent)

The total number of HHF events was lower in the empagliflozin group than in the placebo group with 407 events and 541 events, respectively. The mean cumulative incidence of HHF in the empagliflozin and placebo groups started to diverge shortly after randomisation and continued to segregate further over the course of the trial (Figure 9). Primary analysis using joint frailty model with CV death as a competing risk demonstrated that the risk of total (first and recurrent) HHF was significantly reduced with empagliflozin relative to placebo (HR, 0.73; 95% CI, 0.61 to 0.88, p=0.0009). The hazard of total HHF (first and recurrent) was positively correlated to that of CV death, as indicated by a frailty exponent greater than zero (data not shown).

Figure 9. Key secondary outcome: Total number of HHF (first and recurrent)



Abbreviations: CI, confidence interval; HHF, hospitalisation for heart failure.
Source: Figure 3, Anker et al 2021 (4).

The results of the sensitivity analyses were consistent with the results of the primary analysis for the occurrence of adjudicated HHF (first and recurrent) (Table 20).

Table 20. Sensitivity analyses for the key secondary endpoint: total HHF

Sensitivity analyses	HR (95% CI)
Joint frailty model considering CV death as competing risk (primary analysis model)	0.73 (0.61 – 0.88)
Parametric joint gamma frailty model considering CV death as competing risk	0.73 (0.61-0.88)
Joint frailty model considering AC mortality as competing risk	0.75 (0.62-0.90)
Negative binomial model[a]	0.73 (0.60-0.89)
Negative binomial model without covariate adjustment[a]	0.74 (0.61-0.90)
Cox regression for time to first adjudicated HHF	0.71 (0.60-0.83)

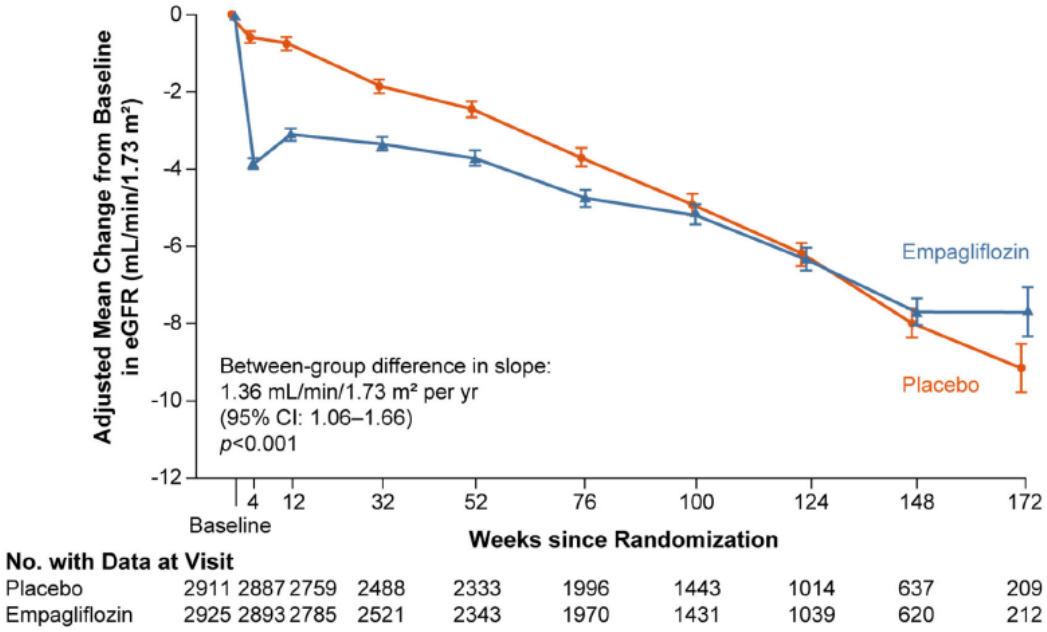
Abbreviations: CV, cardiovascular; HHF, hospitalisation for heart failure; RS, randomised set; TS, treated set.
[a]Rate ratio is shown
Joint frailty model by Rogers et al. (2016) (171).
Source: Table S4, Anker et al 2021 (4).

B.3.6.2.2 Deterioration of renal function

The other key secondary endpoint in the hierarchical testing procedure was mean slope of change in eGFR (mL/min/1.73 m^2) from baseline. Estimation of glomerular filtration rate (GFR) was based on (CKD-EPI)cr (172).

The primary analysis included only “on-treatment” data from the treated set (TS) and measurements up to one day after the last intake of study medication. In the empagliflozin group, the estimated slope was -1.25 ± 0.11 mL/min/1.73 m^2 per year. In the placebo group, eGFR declined more steeply over the duration of the treatment period, with an estimated slope of -2.62 ± 0.11 mL/min/1.73 m^2 per year. The estimated between-group difference in mean slope was 1.36 mL/min/1.73 m^2 per year (95% CI, 1.06 to 1.66; p<0.0001) (Figure 10). In the RS, the adjusted mean eGFR change from baseline to follow-up was 2.4 (95% CI, 1.6 to 3.2) mL/min/1.73m^2 per year for empagliflozin *versus* placebo.

Figure 10. Changes in the estimated GFR, based on the TS and measurements up to one day after the last intake of study medication



Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MMRM, mixed model for repeated measures; TS, treated set.
Notes: Graph shows the adjusted mean changes from baseline in the eGFR as calculated using the CKD Epidemiology Collaboration equation. The bars indicate the standard error. The on-treatment data were analysed with MMRM. Age, baseline eGFR and LVEF were included as linear covariates, while sex, region, baseline diabetes status, last projected visit based on dates of randomisation and trial closure, baseline eGFR according to visit, and visit according to treatment interactions were included as fixed effects.
Source: Figure S4, Anker et al 2021 (4).

Thus, when measurements of renal function were compared at the start and after the discontinuation of empagliflozin and placebo, the eGFR declined significantly more in the placebo group than in the empagliflozin group, leading to increased risk of serious renal outcomes, as described in more detail in Section B.3.6.2.3 Time to composite renal outcome. The initial dip in eGFR seen at the start of the treatment with

empagliflozin represents a reversible functional change in intrarenal haemodynamic commonly observed with SGLT2is and is not associated with an excess risk of investigator-reported acute kidney injury, regardless of presence of CKD (173, 174).

B.3.6.2.3 Time to composite renal outcome

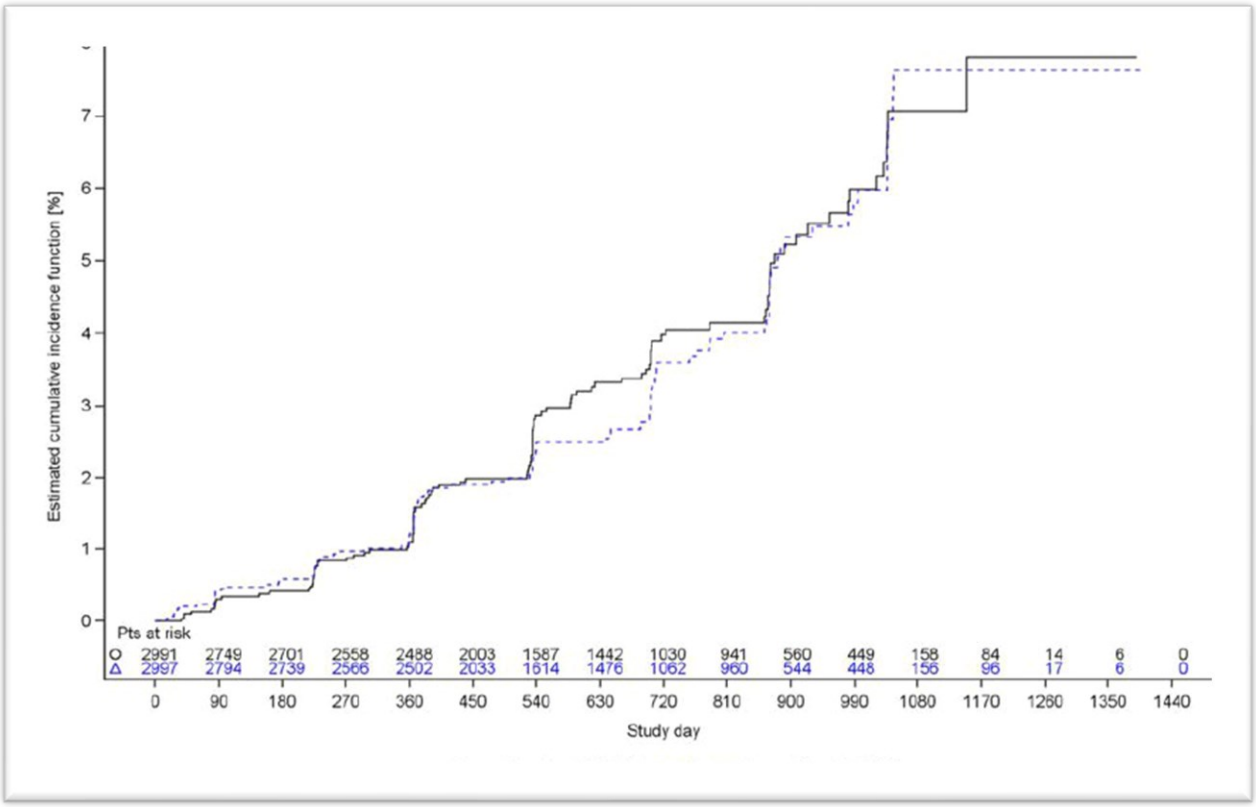
The composite renal endpoint occurred in 108 patients (3.6%) in the empagliflozin group and 112 patients (3.7%) in the placebo group, with the sustained reduction in eGFR from baseline of ≥40% being the first recorded renal event in most patients (Table 21). The risk of the composite renal endpoint was similar between the empagliflozin and the placebo treatment group (HR, 0.95; 95% CI, 0.73 to 1.24; nominal p=0.7243). The estimated cumulative incidence function for the time to the first event of the composite renal endpoint (considering AC mortality as a competing risk) is shown in Figure 11.

Table 21. Cox regression analysis of time to first renal event[a] in all randomised patients

Time to composite renal outcome[b]	Empagliflozin (N=2,997)	Placebo (N=2,991)
Patients with the composite renal endpoint, N (%)	108 (3.6)	112 (3.7)
Only sustained eGFR reduction ≥40% as the first event	95 (3.2)	102 (3.4)
Chronic dialysis as the first event	10 (0.3)	8 (0.3)
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	3 (0.1)	2 (0.1)
Incidence rate per 100 years at risk	2.13	2.23
HR *vs.* placebo (95% CI), composite renal outcome	0.95 (0.73, 1.24)	
Nominal p-value	0.7243	

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.
[a]Cox regression model included covariates age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment.
[b]The composite renal endpoint was comprised of 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 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2, or sustained eGFR <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^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).
Source: EMPEROR-Preserved CSR, Table 11.1.2.6: 1 (166).

Figure 11. Estimated cumulative incidence function for time to the first event of the composite renal endpoint in all randomised patients

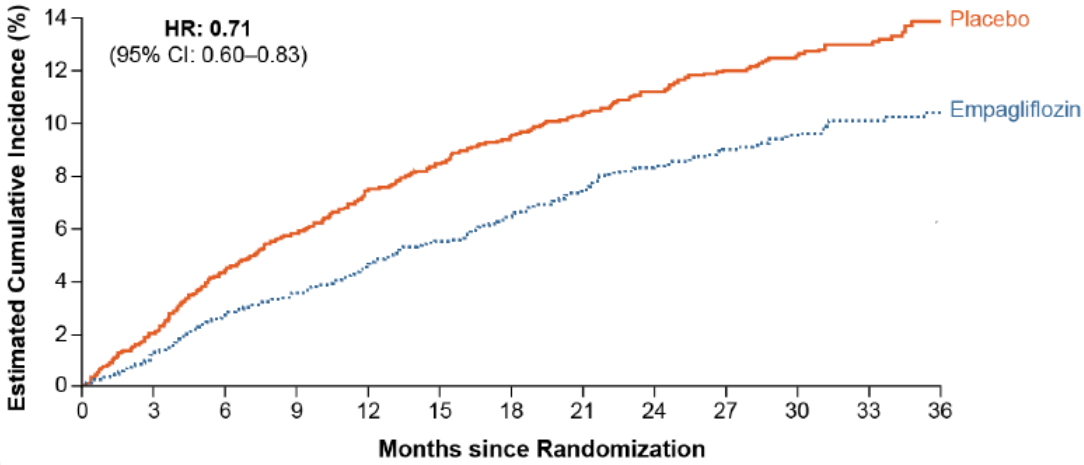


Source: EMPEROR-Preserved CSR, Figure 11.1.2.6.1: 1 (166).

B.3.6.2.4 Time to first adjudicated HHF

Over the duration of the trial, fewer patients experienced the event of first adjudicated HHF in the empagliflozin group (259 of 2,997, 8.6%) compared to placebo group (352 of 2,991, 11.8%). The estimated cumulative incidence of first adjudicated HHF, considering AC mortality as a competing risk, started to diverge between empagliflozin and placebo groups shortly after randomisation and continued to separate over the course of the trial (Figure 12). The risk of adjudicated HHF was significantly reduced with empagliflozin treatment *versus* placebo (HR, 0.71; 95% CI, 0.60 to 0.83; nominal p<0.0001), as determined by the Cox regression model adjusted for age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, gender, baseline LVEF, and treatment.

Figure 12. Time to the first adjudicated HHF



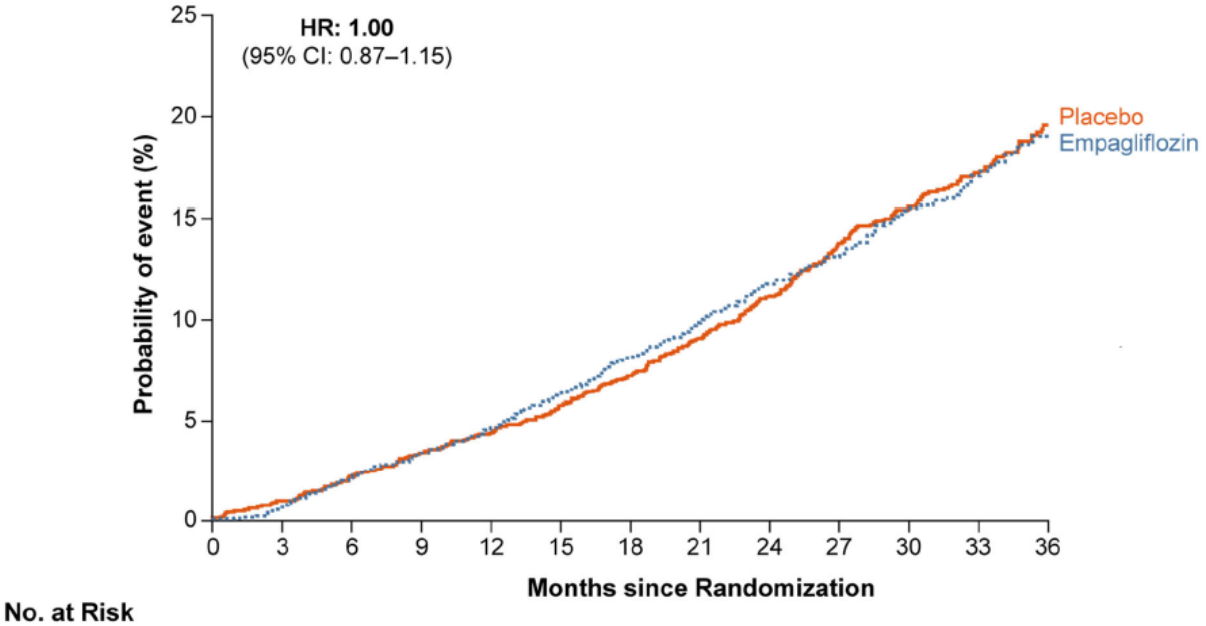
No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Source: Figure S3, Anker et al 2021 (4).

B.3.6.2.5 All-cause mortality

The Kaplan-Meier estimate of time to AC mortality in the RS is shown in Figure 13. Death from any cause occurred in 422 patients (14.1%) in the empagliflozin group and 427 patients (14.3%) in the placebo group. Cox regression of time to AC mortality data for all randomised patients showed that the risk of death from any cause was of equivalence (HR, 1.00; 95% CI, 0.87 to 1.15) and the difference did not reach statistical significance (p=0.9893).

Figure 13. Kaplan-Meier estimate of time to AC mortality in all randomised patients



No. at Risk													
Placebo	2991	2960	2923	2883	2849	2656	2302	2046	1738	1459	1107	781	471
Empagliflozin	2997	2974	2930	2891	2847	2641	2287	2022	1725	1469	1118	794	462

Source: Figure S5, Anker et al 2021 (4).

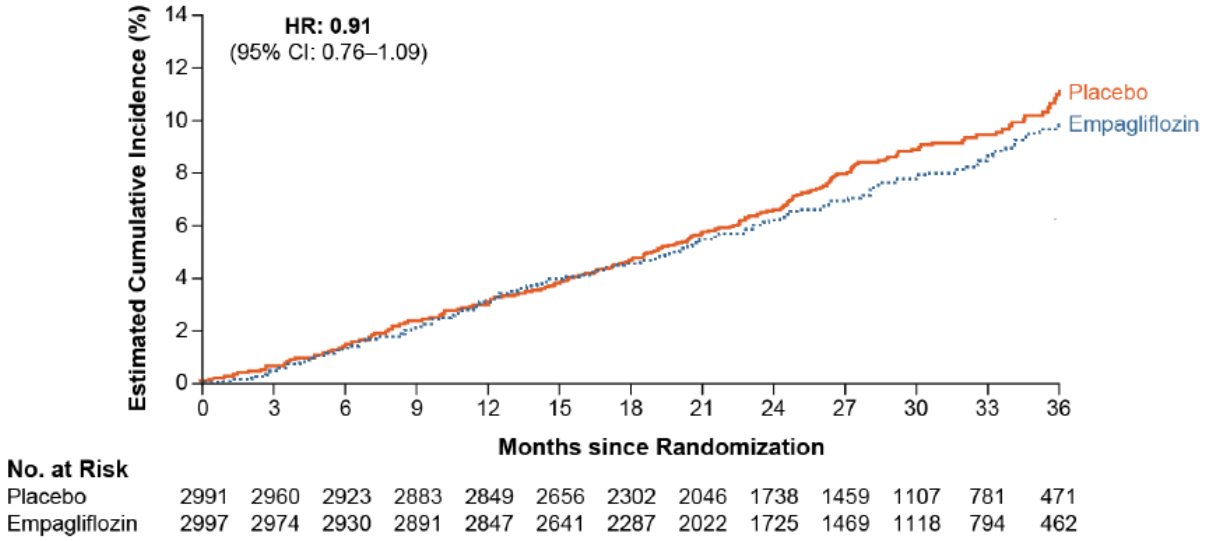
B.3.6.2.6 Cardiovascular mortality

Most of the deaths recorded during the study were due to CV causes, such as sudden cardiac death or HF. Adjudicated CV death occurred in 219 patients (7.3%) in the empagliflozin group and 244 patients (8.2%) in the placebo group. The risk of CV death was 9.0% lower with empagliflozin relative to placebo (HR, 0.91; 95% CI, 0.76 to 1.09), a difference that did not reach statistical significance (p=0.30). As mentioned earlier, the trial was neither designed nor powered to detect the treatment effect of empagliflozin compared to placebo for CV mortality. The cumulative incidence of adjudicated CV death in randomised patients, considering non-CV death as a competing risk, is shown in Figure 14.

Similar to EMPEROR-Preserved, the DELIVER trial was not powered to detect a treatment effect of dapagliflozin compared to placebo for CV mortality, and the identified HR was favourable for dapagliflozin but not statistically significant (HR= 0.88, 95%CI= 0.74–1.05) (10). Nevertheless, an independent meta-analysis including 12,251 patients from the EMPEROR-Preserved and DELIVER trials showed a

reduction in composite CV mortality or HHF (HR= 0.80, 95% CI= 0.30–0.87) (11). More details on the meta-analysis are presented in section B.3.8.

Figure 14. Cardiovascular death

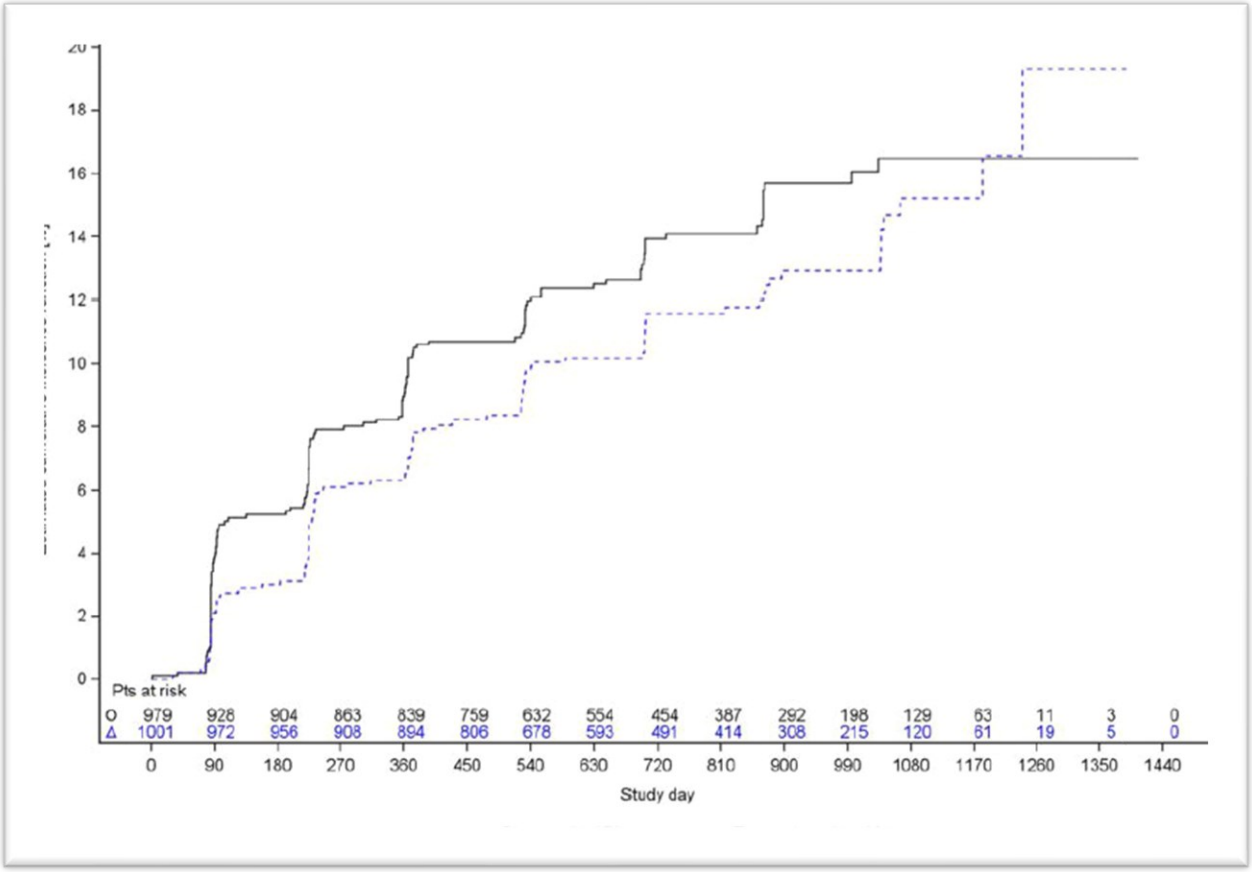


Abbreviation: CI, confidence interval; HR, hazard ratio.
Source: Figure S3, Anker et al 2021 (4).

B.3.6.2.7 Time to onset of diabetes mellitus (DM) in patients with pre-DM

The onset of DM in patients with pre-DM occurred in 120 of 1,001 patients in the empagliflozin group (12.0%) and 137 of 979 patients (14.0%) in the placebo group. The observed reduction in risk of onset of DM with empagliflozin compared to placebo (HR, 0.84; 95% CI, 0.65 to 1.07) was not statistically significant (nominal p=0.15). The estimated cumulative incidence of time to onset of DM in patients with pre-DM, considering AC mortality as a competing risk, started to diverge after approximately 3 months, and was maintained over the remainder of the trial (Figure 15).

Figure 15. Estimated cumulative incidence function for time to onset of DM in patients with baseline pre-DM in the randomised set



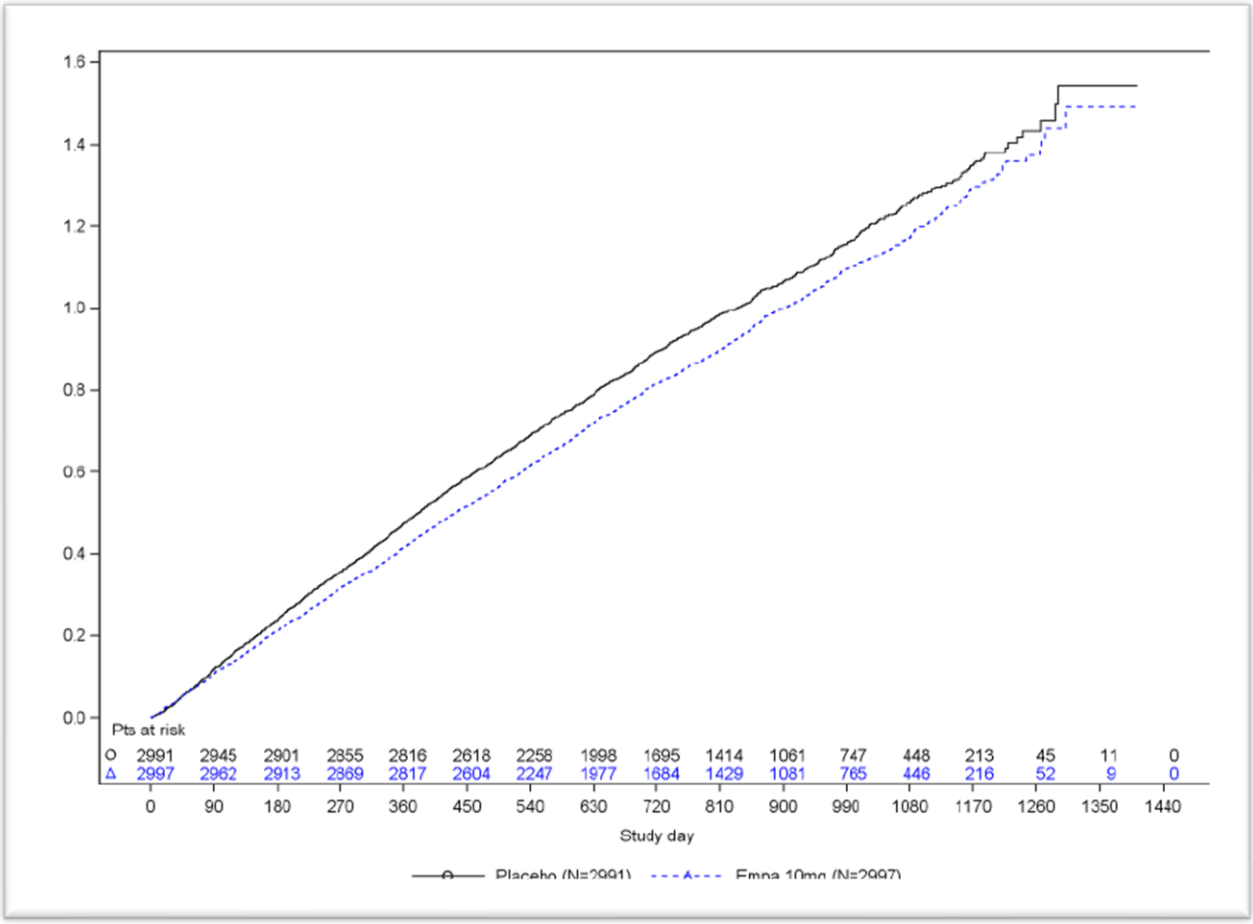
Source: EMPEROR-Preserved CSR, Figure 11.1.2.8.1: 1 (166).

B.3.6.2.8 First and recurrent all-cause hospitalisation

All-cause (AC) hospitalisation occurred in 42.4% (1,271 of 2,997) of patients in the empagliflozin group and 44.8% (1,340 of 2,991) in the placebo group. The total number of hospitalisation events was lower in the empagliflozin group (2,566) than in the placebo group (2,769). Analysis of this endpoint using a joint frailty model that accounts for the dependence between recurrent AC hospitalisation and AC mortality demonstrated that the risk of recurrent AC hospitalisation was reduced with empagliflozin treatment compared to placebo (HR, 0.93; 95% CI, 0.85 to 1.01; nominal p=0.10). The mean cumulative incidence curves of AC hospitalisation in empagliflozin and placebo groups diverged at about 90 days after randomisation and maintained their separation throughout the study (Figure 16). Cox regression showed 2.33%

reduction in risk of first AC hospitalisation with empagliflozin compared to placebo (HR, 0.92; 95% CI, 0.85 to 0.99; p=0.03).

Figure 16. Mean cumulative function for occurrence of AC hospitalisation (first and recurrent) in the randomised set



Source: EMPEROR-Preserved CSR, Figure 11.1.2.5.1: 1 (166).

B.3.6.2.9 Further secondary clinical endpoints

Results of further exploratory secondary endpoints from EMPEROR-Preserved trial, including measurement of health status by KCCQ, are presented in Table 22.

Table 22. Summary of further exploratory secondary endpoints from EMPEROR-Preserved study

Endpoint	Empagliflozin (N=2,997)	Placebo (N=2,991)
Time to adjudicated MI (fatal or non-fatal), RS		
Patients with MI, N (%)	49 (1.6)	40 (1.3)

Endpoint	Empagliflozin (N=2,997)	Placebo (N=2,991)
Incidence rate per 100 years at risk	0.78	0.64
HR vs placebo (95% CI)	1.23 (0.81-1.86)	
Nominal p-value	0.34	
Time to adjudicated stroke (fatal or non-fatal), RS		
Patients with stroke, N (%)	92 (3.1)	84 (2.8)
Ischaemic	83 (2.8)	74 (2.5)
Haemorrhagic	7 (0.2)	8 (0.3)
Unclassified	2 (0.1)	2 (0.1)
Incidence rate per 100 years at risk	1.48	1.35
HR vs placebo (95% CI)	1.10 (0.82-1.47)	
Nominal p-value	0.54	
Patients with fatal stroke	19 (0.6)	20 (0.7)
Time to new onset of Afib, as ECG finding or as AE, RS		
Patients without baseline or history of Afib[a], N (%)	1,454 (100%)	1,477 (100%)
Patients with new onset of Afib, N (%)	116 (8.0)	119 (8.1)
Incidence rate per 100 years at risk	3.95	4.04
HR vs placebo (95% CI)	1.00 (0.77 to 1.29)	
Nominal p-value	0.98	
Blood pressure (mm Hg) changes from baseline to week 52 (mm Hg), RS		
Systolic blood pressure change	-1.8±0.3	-0.6±0.3
Adjusted mean difference (95% CI)	-1.2 (-2.1 to -0.3)	
p-value	0.01	
Diastolic blood pressure change	-0.9±0.2	-0.7±0.2

Endpoint	Empagliflozin (N=2,997)	Placebo (N=2,991)
Adjusted mean difference (95% CI)	-0.2 (-0.7 to 0.3)	
p-value	0.46	
HbA1c (%) change from baseline to week 52, RS patients with diabetes		
Adjusted mean change from baseline	-0.16±0.02	-0.03±0.02
Adjusted mean difference (95% CI)	-0.19 (-0.25 to -0.14)	
p-value	<0.0001	
Body weight (kg) change from baseline to week 52, RS		
Adjusted mean change from baseline	-1.39±0.09	-0.11±0.09
Adjusted mean difference (95% CI)	-1.28 (-1.54 to -1.03)	
p-value	<0.0001	
Haematocrit (%) change from baseline to week 52, RS		
Adjusted mean change from baseline	1.94±0.07	-0.41±0.07
Adjusted mean difference (95% CI)	2.36 (2.17 to 2.54)	
p-value	<0.0001	
NT-proBNP (pg/mL) change from baseline to week 52, RS		
Adjusted median change from baseline (IQR)	-29 (-335 to 263)	-9 (-286 to 322)
Adjusted geometric mean ratio	0.95 (0.91 to 0.99)	
p-value	0.01	
Uric acid (mg/dL) change from baseline to week 52, RS		
Adjusted mean change from baseline	-0.90±0.03	-0.10±0.03
Adjusted mean difference (95% CI)	-0.80 (-0.88 to -0.72)	
p-value	<0.0001	

Endpoint	Empagliflozin (N=2,997)	Placebo (N=2,991)
QoL measured by KCCQ at 52 weeks[b], TS		
Change in clinical summary score at 52 weeks	4.51±0.31	3.18±0.31
Adjusted mean change from baseline (95% CI)	1.32 (0.45 to 2.19)	
Nominal p-value	0.0028	
Change in overall summary score at 52 weeks	5.03±0.30	3.66±0.31
Adjusted mean change from baseline (95% CI)	1.37 (0.52 to 2.21)	
Nominal p-value	0.0015	
Change in total symptom score at 52 weeks	5.89±0.34	3.95±0.34
Adjusted mean change from baseline (95% CI)	1.94 (1.01 to 2.88)	
Nominal p-value	<0.0001	

Abbreviations: AE, adverse event; Afib, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HbA1c, glycated haemoglobin; HR, hazard ratio; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; QoL, quality of life; RS, randomised set; SE, standard error; TS, treated set.
Note: Plus-minus values are means ± SE. Estimates of effect size for time to event endpoints (HR, 95% CI) were derived for the randomised set using Cox regression model which included covariates age, baseline eGFR (CKD-EPI)cr, region, baseline diabetes status, sex, baseline LVEF, and treatment. Continuous endpoints (blood pressure, KCCQ scores) were analysed using mixed model for repeated measures (MMRM).
[a]Based on investigator-reported medical history or baseline ECG.
[b]The clinical summary score on the Kansas City Cardiomyopathy Questionnaire ranges from 0 to 100, with higher scores indicating a better quality of life. Analysis of PRO data with a MMRM was based on the treated set and using on-treatment values only.
Source: Table 11.1.3.1:1, Table 15.2.4.2.1, Sections 11.1.2.7, 11.1.2.8.2 and 11.1.3.4, EMPEROR-Preserved CSR (166); Table S5, Anker et al 2021 (4).

Frequency of MI, stroke and atrial fibrillation were similar between the two treatment groups as based on Cox regression analysis and estimated cumulative incidence analysis. 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 to -0.3) for systolic and -0.2 mmHg (95% CI, -0.7 to 0.3) for diastolic blood pressure.

The change from baseline in health status was assessed by the KCCQ-CSS at week 52. The clinical summary score measures HF symptom frequency, symptom burden, and physical limitations. There was a greater improvement in the clinical summary

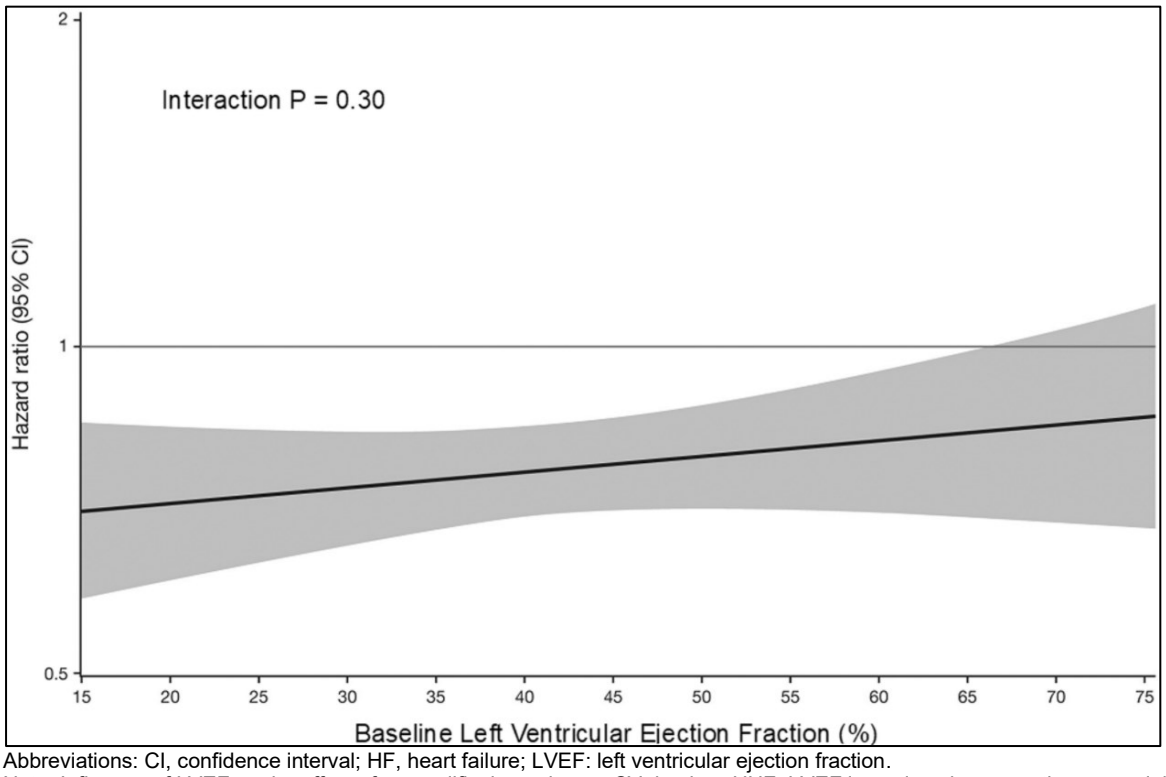
score from baseline in the empagliflozin group than in the placebo group at week 52. A similar improvement was also observed for the Kansas City Cardiomyopathy Questionnaire - total symptom score (KCCQ-TSS) and Kansas City Cardiomyopathy Questionnaire - overall summary score (KCCQ-OSS), as well as for the individual domains ‘quality of life’ and ‘social limitation’. There were no relevant differences between the treatment groups with regards to HRQoL as assessed by the EQ-5D-5L questionnaire.

B.3.6.3 Effect of empagliflozin in patients with HF across spectrum of LVEF

A combined HF analysis stratified by LVEF was performed on both the EMPEROR-Reduced and EMPEROR-Preserved trials (9,718 patients; 4,860 empagliflozin and 4,858 placebo) (145). Both trials had pre-specified subgroup analysis based on LVEF but a more granular stratification was done post hoc in this analysis. The patients were divided into six groups categorised by LVEF: <25%, 25–34%, 35–44%, 45–54%, 55–64%, and ≥65% in order to have a better understanding of the effect of empagliflozin across the full range of chronic HF patients (145).

The combined analysis demonstrated heterogeneity in the baseline characteristics across the LVEF groups. Patients with higher EF were mostly older females with greater comorbidity burden (145). In terms of efficacy, empagliflozin consistently reduced the primary composite endpoint of time to CV death or first HHF for HF patients across a broad spectrum of LVEF (Figure 17). The benefit is mostly driven by the effect of empagliflozin on time to first HHF and total (first and recurrent) HHF in patients with EF ranging from <25% to <65%. The pattern of effects of empagliflozin across the LVEF intervals were similar for both genders. In another study, the benefit of empagliflozin on worsening HF events first reached statistical significance at 18 days after randomization and maintained significance thereafter (110). The combined analysis also showed that the improvement in patients’ quality of life as measured by KCCQ-CSS had similar patterns as the HF outcomes. In conclusion, irrespective of differences in the demographic characteristics, the benefit of empagliflozin on HF outcomes and health status were consistently observed across the broad spectrum of LVEF. This effect was also demonstrated in the meta-analysis of EMPEROR-Preserved and DELIVER trials (11), as detailed in section B.3.8.

Figure 17. Effect of empagliflozin on primary composite endpoint in patients with HF across spectrum of LVEF



Abbreviations: CI, confidence interval; HF, heart failure; LVEF: left ventricular ejection fraction.
Note: Influence of LVEF on the effect of empagliflozin on time to CV death or HHF. LVEF is analysed as a continuous variable, based on the assumption that the relationship is linear. Analysis of the influence of LVEF using cubic splines yielded a pattern similar to that observed in our six subgroups, showing a consistent risk reduction in patients with an EF <65% and an attenuated effect at the highest ejection fractions.
Shaded areas represent 95% confidence intervals.
Reference: Butler et. al. (2022) (145).

B.3.7 Subgroup analysis

Results of the clinically relevant pre-specified subgroups can be found in Appendix E. It is to be noted that subgroup analyses were not adjusted for multiple testing. Hence, the subgroup findings were not specifically powered and were regarded as hypothesis generating (Appendix E).

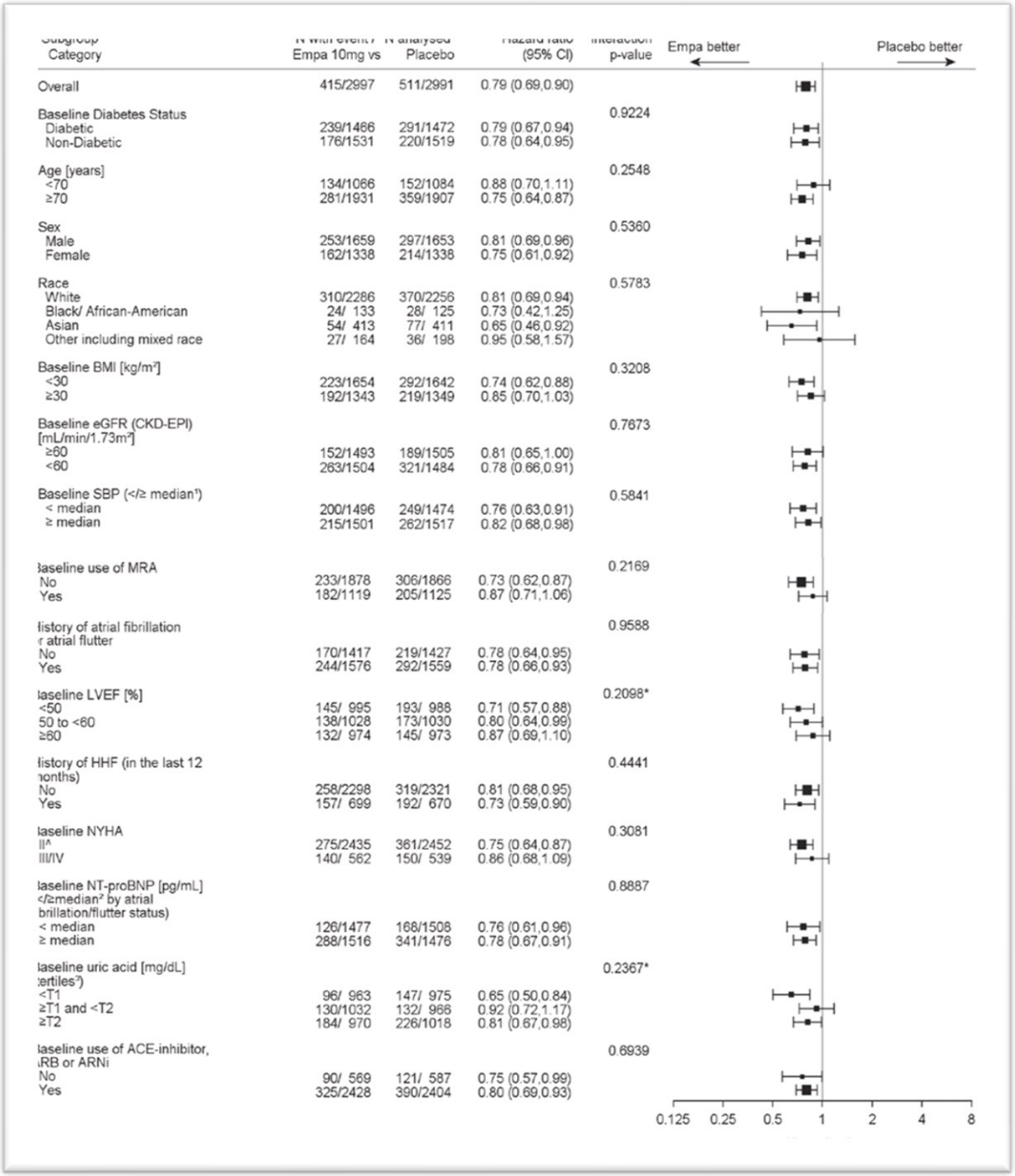
The pre-specified subgroup analyses for the efficacy endpoints of EMPEROR-Preserved were:

- Diabetes at baseline (diabetic, non-diabetic patients)
- Age (<70 years and ≥70 years)
- Gender
- Race (White, Black, Asian, other)
- BMI (<30 kg/m^2 and ≥30 kg/m^2)

- Renal function at baseline (eGFR ≥60 mL/min/1.73 m^2, <60 mL/min/1.73 m^2)
- SBP at baseline
- Baseline use of mineralocorticoid receptor antagonist
- History of AF
- HF physiology (reflected in baseline LVEF and level of NT-pro-BNP)
- HHF in the last 12 months
- NYHA at baseline (II, III/IV)
- Uric acid, in thirds, at baseline
- Baseline use of ACEI, ARB, or ARNI at baseline
- Geographic region (Asia, Europe, Latin America, North America, and other)

No significant variation in treatment effect was seen across pre-specified subgroups as the point estimate HR remained less than one across subgroups (Figure 18). Therefore, it is not anticipated that the technology would differ by subgroup in the health benefits it offers and its costs versus dapagliflozin compared to the full population.

Figure 18. Primary outcome of EMPEROR-Preserved in pre-specified subgroups



Subgroup Category	N with event / N analysed Empa 10mg vs	Placebo	Hazard ratio (95% CI)	Interaction p-value
Overall	415/2997	511/2991	0.79 (0.69,0.90)	
Baseline Diabetes Status				0.9224
Diabetic	239/1466	291/1472	0.79 (0.67,0.94)	
Non-Diabetic	176/1531	220/1519	0.78 (0.64,0.95)	
Age [years]				0.2548
<70	134/1066	152/1084	0.88 (0.70,1.11)	
≥70	281/1931	359/1907	0.75 (0.64,0.87)	
Sex				0.5360
Male	253/1659	297/1653	0.81 (0.69,0.96)	
Female	162/1338	214/1338	0.75 (0.61,0.92)	
Race				0.5783
White	310/2286	370/2256	0.81 (0.69,0.94)	
Black/ African-American	24/ 133	28/ 125	0.73 (0.42,1.25)	
Asian	54/ 413	77/ 411	0.65 (0.46,0.92)	
Other including mixed race	27/ 164	36/ 198	0.95 (0.58,1.57)	
Baseline BMI [kg/m²]				0.3208
<30	223/1654	292/1642	0.74 (0.62,0.88)	
≥30	192/1343	219/1349	0.85 (0.70,1.03)	
Baseline eGFR (CKD-EPI) [mL/min/1.73m²]				0.7673
≥60	152/1493	189/1505	0.81 (0.65,1.00)	
<60	263/1504	321/1484	0.78 (0.66,0.91)	
Baseline SBP (</≥ median[1])				0.5841
< median	200/1496	249/1474	0.76 (0.63,0.91)	
≥ median	215/1501	262/1517	0.82 (0.68,0.98)	
Baseline use of MRA				0.2169
No	233/1878	306/1866	0.73 (0.62,0.87)	
Yes	182/1119	205/1125	0.87 (0.71,1.06)	
History of atrial fibrillation or atrial flutter				0.9588
No	170/1417	219/1427	0.78 (0.64,0.95)	
Yes	244/1576	292/1559	0.78 (0.66,0.93)	
Baseline LVEF [%]				0.2098*
<50	145/ 995	193/ 988	0.71 (0.57,0.88)	
50 to <60	138/1028	173/1030	0.80 (0.64,0.99)	
≥60	132/ 974	145/ 973	0.87 (0.69,1.10)	
History of HHF (in the last 12 months)				0.4441
No	258/2298	319/2321	0.81 (0.68,0.95)	
Yes	157/ 699	192/ 670	0.73 (0.59,0.90)	
Baseline NYHA				0.3081
II^	275/2435	361/2452	0.75 (0.64,0.87)	
III/IV	140/ 562	150/ 539	0.86 (0.68,1.09)	
Baseline NT-proBNP [pg/mL] </≥median[2] by atrial fibrillation/flutter status)				0.8887
< median	126/1477	168/1508	0.76 (0.61,0.96)	
≥ median	288/1516	341/1476	0.78 (0.67,0.91)	
Baseline uric acid [mg/dL] tertiles[3])				0.2367*
<T1	96/ 963	147/ 975	0.65 (0.50,0.84)	
≥T1 and <T2	130/1032	132/ 966	0.92 (0.72,1.17)	
≥T2	184/ 970	226/1018	0.81 (0.67,0.98)	
Baseline use of ACE-inhibitor, ARB or ARNi				0.6939
No	90/ 569	121/ 587	0.75 (0.57,0.99)	
Yes	325/2428	390/2404	0.80 (0.69,0.93)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HHF, hospitalisation for heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

Note: The size of the squares for the hazard ratios is proportional to the size of the subgroup. Interaction p values are nominal; the subgroup analyses were not adjusted for multiple testing. The BMI is the weight in kilograms divided by the square of the height in metres. Race was reported by the patients.

^Patients with NYHA class I are counted in subgroup NYHA class II.

[1]Baseline SBP median: 132 [mmHg].

[2]Baseline NT-proBNP median for patients with history of atrial fibrillation or AF: 1354 [pg/mL].

[2]Baseline NT-proBNP median for patients without history of atrial fibrillation or AF: 614 [pg/mL].

[3]Baseline uric acid tertile cut-offs for males are T1: 5.9 T2: 7.5 [mg/dL] [rounded].

[3]Baseline uric acid tertile cut-offs for females are T1: 5.4 T2: 6.9 [mg/dL] [rounded].
*= Trend test
Source: EMPEROR-Preserved CSR, Figure 11.1.1.3: 1 (166).

B.3.8 Meta-analysis

A recent independent meta-analysis examined the clinical efficacy of SGLT2i treatments for patients with chronic HF and mildly reduced or preserved ejection fraction (11). The authors included 12,251 patients from the EMPEROR-Preserved and DELIVER trials, in a fixed-effects meta-analysis. The results for the composite CV mortality or HHF were favourable for the SGLT2i treatments (HR= 0.80, 95% CI= 0.30–0.87). When considering each outcome separately, the results were again positive for the SGLT2i treatments, with an HR for CV mortality of 0.88 (95%CI= 0.77–1.00) and 0.74 (95%CI= 0.67–0.83 for HHF). The authors of the meta-analysis concluded that empagliflozin and dapagliflozin reduce the risk of CV mortality and HHF, and therefore offer two important treatment options for HF patients with a historically high unmet need (i.e., HF with LVEF>40%).

B.3.9 Indirect and mixed treatment comparisons

- Until recently, there was no licensed treatment for chronic HF with preserved or mildly reduced EF in adults.
- In June 2023, dapagliflozin was recommended by NICE, within its MA, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902) on the basis of the DELIVER trial.
- Therefore, the only available comparator for empagliflozin is dapagliflozin for chronic HF with preserved or mildly reduced EF in adults.
- An ITC feasibility assessment was conducted for the EMPEROR-Preserved and DELIVER trials, which concluded that the EMPEROR-Preserved and DELIVER trials were very similar in terms of inclusion and exclusion criteria, study design, outcomes included, and patients' baseline characteristics. This is further supported by an independent meta-analysis of these two trials as published by Vaduganathan et al. 2022 (11).

- A Bucher analysis was therefore the most appropriate method for comparing empagliflozin and dapagliflozin, the results of which showed that there is no statistically significant difference between the two drugs in clinical efficacy. This finding is supported by clinical validation performed by the company (see section B.4.2.5), the drugs can be considered equally effective.

Feasibility assessment

As discussed in section B.1.3.2.2 , there is a high unmet need for effective treatments for patients with chronic HF with preserved or mildly reduced EF. In June 2023, dapagliflozin was recommended by NICE, within its MA, as a treatment option for this condition (TA902), and it is the only other licensed treatment for this condition other than empagliflozin (8). Therefore, dapagliflozin is the only relevant comparator for empagliflozin for treating patients with chronic HF with preserved or mildly reduced EF.

A feasibility assessment was performed for the EMPEROR-Preserved and DELIVER trials. The feasibility assessment aimed to establish whether an ITC (e.g., Bucher, NMA, MAIC) was possible in consideration of data availability and between-study heterogeneity in terms of study design as well as patient demographic and disease characteristics.

The following activities were undertaken as part of the feasibility assessment:

- Assessing whether a connected network of evidence for a given outcome of interest can be established; this was accomplished by checking the availability of consistently reported data for each outcome of interest and drawing network diagrams showing how all direct and indirect evidence is connected.

- Assessing whether the evidence for a given outcome of interest can be pooled across the studies within each treatment group; this was accomplished by checking the availability of reported data for each outcome of interest,

consistency of outcome definitions and methods of outcome measurement or ascertainment.

- Assessing whether the comparability/transitivity assumption holds; since within-trial but not between-trial randomisation is preserved in NMA, studies deemed eligible for evidence synthesis were assessed for presence and extent of clinical and methodological heterogeneity between-studies comparing different treatments, chiefly comprising:
    - A comparison of baseline patients' characteristics (e.g., age, performance status, histology, number of previous treatments) to assess the comparability of study populations in all included trials;
    - A comparison of outcome definitions;
    - A comparison of doses, dosing schedules and administration routes of a given treatment investigated in different trials;
    - A comparison of study design and quality of all included trials to identify potential sources of bias that impact the outcomes of interest.

Findings from feasibility assessment

Given that only two trials were of interest for this ITC, an NMA was ruled out as a potential method for comparison between empagliflozin and dapagliflozin because a network of studies requires more than two trials.

The study design implemented in the EMPEROR-Preserved and DELIVER trials was very similar. Both studies were phase III, randomised, double-blind, placebo-controlled trials with parallel assignment. The sample size of the two trials was similar, and both recruited a similar target population, i.e., adults with chronic HF NYHA class II-IV and LVEF >40% (Table 23). The main difference between the two trials is in the inclusion of 18% of patients with previous LVEF≤40% which had then improved (i.e., LVEF>40%) in the DELIVER trial, while EMPEROR-Preserved did not include patients with previous LVEF≤40%. As part of the DELIVER trial, subgroup analyses were

performed separately for the primary endpoint for patients without and with previous LVEF≤40%. For both subgroups, dapagliflozin was found to be statistically significantly more efficacious compared to background therapy (i.e., without previous LVEF≤40%: HR= 0.84, 95%CI=0.73-0.95; with previous LVEF≤40%: HR= 0.74, 95%CI=0.56-0.97) (10). The inclusion of patients with previous LVEF≤40% was also noted by the appraisal committee for dapagliflozin in NICE TA902. The committee recognised that patients with previous LVEF≤40% were included in DELIVER but ultimately concluded that the inclusion of these patients did not impact the generalisability of DELIVER results to the NHS setting. Given the consistency in the statistically significant finding for the DELIVER trial despite previous LVEF≤40% and the committee's conclusion regarding its generalisability to the target population in the NHS, the populations of EMPEROR-Preserved and DELIVER trials are deemed comparable for the purposes of this ITC.

Table 23. Comparison of baseline patient characteristics in EMPEROR-Preserved and DELIVER

	EMPEROR-Preserved		DELIVER	
Baseline characteristic	**Empagliflozin (N = 2,997)**	**Placebo (N = 2,991)**	**Dapagliflozin (N = 3,131)**	**Placebo (N = 3,132)**
Age, mean (SD)	71.8 (9.3)	71.9 (9.6)	71.8 (9.6)	71.5 (9.5)
Female sex, n (%)	1338 (44.6)	1338 (44.7)	1364 (43.6)	1383 (44.2)
BMI, mean (SD)	29.77 (5.8)	29.9 (5.9)	29.8 (6.2)	29.9 (6.1)
Race				
White, n (%)	2286 (76.3)	2256 (75.4)	2214 (70.7)	2225 (71)
Black, n (%)	133 (4.4)	125 (4.2)	81 (2.6)	78 (2.5)
Asian, n (%)	413 (13.8)	411 (13.7)	630 (20.1)	644 (20.6)
Other race, n (%)	165 (5.5)	199 (6.7)	206 (6.6)	185 (5.9)
Region				
North America, n (%)	360 (12)	359 (12)	428 (13.7)	423 (13.5)
South/Latin America, n (%)	758 (25.3)	757 (25.3)	602 (19.2)	579 (18.5)
Europe, n (%)	1346 (44.9)	1343 (44.9)	1494 (47.7)	1511 (48.2)
Asia, n (%)	343 (11.4)	343 (11.5)	607 (19.4)	619 (19.8)
Other, n (%)	190 (6.3)	189 (6.3)	-	-
NYHA functional classification				
I, n (%)	3 (0.1)	1 (<0.1)	-	1 (<0.1)
II, n (%)	2432 (81.1)	2451 (81.9)	2314 (73.9)	2399 (76.6)
III, n (%)	552 (18.4)	531 (17.8)	807 (25.8)	724 (23.1)
IV, n (%)	10 (0.3)	8 (0.3)	10 (0.3)	8 (0.3)
Heart rate – beats/min, mean (SD)	70.4 (12)	70.3 (11.8)	72 (12)	71 (12)
Systolic blood pressure – mm Hg, mean (SD)	131.8 (15.6)	131.9 (15.7)	128 (15)	128 (15)

LVEF				
LVEF – %, mean (SD)	54.3 (8.8)	54.3 (8.8)	54 (8.6)	54.3 (8.9)
LVEF >40% to <50% — no. (%)	995 (33.2)	988 (33)	1067 (34.1)	1049 (33.5)
LVEF ≥50% to <60% — no. (%)	1028 (34.3))	1030 (34.4)	1133 (36.2)	1123 (35.9)
LVEF ≥60% — no. (%)	974 (32.5)	973 (32.5)	931 (29.7)	960 (30.7)
Medical history				
HHF past 12 months, n (%)	669 (23.3)	670 (22.4)	-	-
Hypertension, n (%)	2721 (90.8)	2703 (90.4)	2755 (88)	2798 (89.3)
DM, n (%)	1466 (48.9)	1472 (49.2)	1401 (44.7)	1405 (44.9)
Previous LVEF ≤40%, n (%)	0	0	572 (18.3)	579 (18.5)
Estimated GFR – ml/min/1.73m2 Mean (SD)	60.6 (19.8)	60.6 (19.9)	61 (19)	61 (19)

Abbreviations: AC, all-cause; BMI, body mass index; CI, confidence intervals; CV, cardiovascular; HHF, hospitalisation due to HF; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation,

In terms of intervention and control arm, both empagliflozin and dapagliflozin were studied in combination with background therapy for symptom management in EMPEROR-Preserved and DELIVER, respectively. The background therapy offered in both trials consisted of a basket of therapies including loop diuretics, ACE inhibitors, and beta-blockers. The outcomes for the placebo + background therapy arms of the two trials were compared, to determine if there were any differences potentially attributed to the background therapy offered. The outcomes for each study are reported in Table 24. Overall, the results show that the two background therapy arms are comparable, and no meaningful differences were noted.

Table 24. Overview of outcomes for the Placebo + background therapy groups in the EMPEROR-Preserved and DELIVER trials

	EMPEROR-Preserved – Placebo arm (N= 2,989)		**DELIVER – Placebo arm (N= 3,132)**	
Outcome	Number of events (%)	Events / 100patient-years	Number of events (%)	Events / 100patient-years
CV death or HHF	511 (17.1%)	8.7	610 (19.5%)	9.6
HHF	352 (11.8%)	6	418 (13.3%)	6.5
CV death	244 (8.2%)	3.8	261 (8.3%)	3.8
AC death	427 (14.3%)	6.7	526 (16.8%)	7.6

Abbreviations: AC, all-cause; CI, confidence intervals; CV, cardiovascular; HHF, hospitalisation due to HF; HR, hazard ratio; LVEF, left ventricular ejection fraction

As described in section B.2.1 and B.3.3.1.5, EMPEROR-Preserved and DELIVER reported similar endpoints. A minor difference was noted in terms of the definition of

the primary endpoint. The composite outcome of CV mortality or HHF in DELIVER included hospitalisation caused by HF or urgent HF visits. In EMPEROR-Preserved, the composite outcome regarded CV mortality or hospitalisation caused by HF. The inclusion of urgent HF visits in the composite endpoint for DELIVER is not likely to influence the comparability of the composite outcomes between the two trials given that urgent HF visits were the rarest clinical event reported (i.e., 60/3131 [0.9 events/100 patient years] and 78/3132 [1.1 events/100 patient years] for dapagliflozin and placebo, respectively); further, the HRs for dapagliflozin vs placebo for HHF and dapagliflozin vs placebo for urgent HF visits were very similar (i.e., 0.77 and 0.76, respectively). In terms of secondary outcomes, both trials reported HHF, CV mortality, AC mortality, facilitating a comparison between empagliflozin and dapagliflozin for secondary endpoints as well.

Based on the feasibility assessment, it was concluded that the EMPEROR-Preserved and DELIVER trials were similar, and an ITC of empagliflozin and dapagliflozin was possible. The Bucher method was selected as the most appropriate method of evidence synthesis based on similarity between the trials, low risk of bias and it preserves randomisation. Further, a frequentist approach using the Bucher method was preferred over a Bayesian approach due to the limited evidence base (n=2 studies). Bucher analysis is used to compare outcomes between two indirect treatments across different studies, where different interventions are compared to a common comparator (i.e., placebo) (175). It assumes that the trials included in the ITC are similar with regards to the study population, study design, and outcome measurements, and the distribution of treatment effect modifiers (i.e., study and patient characteristics that have an independent influence on treatment outcome). The feasibility assessment supports the conclusion that the above assumptions are appropriate.

It is important to note that a MAIC could also be considered as a potential method to establish comparative effectiveness. In this case, a MAIC was not considered appropriate given that there were no clinically meaningful differences between patients' baseline characteristics that would be expected to influence the results. Any differences that were identified would not be feasible for adjustment as they reflect

slight study design modifications in the DELIVER trial which cannot be matched in the EMPEROR-Preserved trial (i.e., inclusion of previously diagnosed LVEF≤40% patients, inclusion of urgent HF visits within the primary endpoint). Furthermore, a MAIC is likely to increase rather than reduce decision making uncertainty as the results will reflect a smaller effective sample size after matching the populations of the two trials. Hence, it was concluded that the conduct of a MAIC would add little to no additional value to inform the comparative effectiveness assessment between dapagliflozin and empagliflozin.

Bucher analyses results

For ease of review, transparency and reproducibility, the Bucher analysis was conducted in Microsoft® Excel, as described by Tobias et al 2014 (176). Bucher analyses were performed in four outcomes: composite outcome (i.e., CV mortality or HHF), HHF (i.e., analysed as time to first HHF), CV mortality, AC mortality. These outcomes were chosen because they include the primary outcome of both trials, and the key secondary outcomes where benefits from both empagliflozin and dapagliflozin have been seen for patients with HF and LVEF >40%, i.e., reducing the risk for HHF and potentially improving patients' survival. In addition, those outcomes were commonly defined and reported for both trials. As shown in Table 25, no statistically significant differences were observed across all endpoints, demonstrating that empagliflozin and dapagliflozin are equally effective for patients with chronic HF with preserved or mildly reduced ejection fraction. In terms of point estimates of the Bucher derived HRs, a favourable treatment effect is shown for empagliflozin for the composite outcome (i.e., CV mortality or HHF) and HHF, while a favourable treatment effect is shown for dapagliflozin for CV death and AC death; this observed inconsistency in treatment effect is further evidence supporting the conclusion that there is no consistent trend favouring either drug.

Table 25. Overview of Bucher analyses results

Analysis	HR (95% CI)	P-value
CV death or HHF*		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.79 (0.69-0.90)	0.001

DELIVER (dapagliflozin vs background therapy)	0.82 (0.73-0.92)	0.001
Empagliflozin vs dapagliflozin	0.96 (0.81-1.15)	0.691
HHF		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.71 (0.60-0.83)	<0.001
DELIVER (dapagliflozin vs background therapy)	0.77 (0.67-0.89)	<0.001
Empagliflozin vs dapagliflozin	0.92 (0.74-1.14)	0.470
CV death		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.91 (0.76-1.09)	0.310
DELIVER (dapagliflozin vs background therapy)	0.88 (0.74-1.05)	0.153
Empagliflozin vs dapagliflozin	1.03 (0.80-1.33)	0.806
AC death		
EMPEROR-Preserved (empagliflozin vs background therapy)	1 (0.87-1.15)	1
DELIVER (dapagliflozin vs background therapy)	0.94 (0.83-1.07)	0.345
Empagliflozin vs dapagliflozin	1.06 (0.88-1.28)	0.531

Abbreviations: AC, all-cause; CI, confidence intervals; CV, cardiovascular; HHF, hospitalisation due to HF; HR, hazard ratio; SoC, standard of care
*In DELIVER, the composite outcome includes urgent HF visits too

B.3.9.1 Uncertainties in the indirect and mixed treatment comparisons

A sensitivity analysis was performed to examine the potential impact of the inclusion of patients with previous LVEF≤40% within the DELIVER trial might have on the Bucher results. In the DELIVER trial publication, only the HR for the composite outcome was provided for subgroup analyses based on previous LVEF≤40% (10). A revised Bucher analysis comparing the composite outcome for the EMPEROR-Preserved ITT population versus the DELIVER population excluding patients with previous LVEF≤40% is presented below, which demonstrates that the HR for empagliflozin vs dapagliflozin has slightly changed in favor of empagliflozin compared to the analysis comprising the ITT population from DELIVER (0.94 [0.78-1.13], p=0.531), while the results remain statistically insignificant (Table 26).

Table 26. Bucher analyses results when patients with previous LVEF≤40% are excluded from DELIVER

Analysis	HR (95% CI)	P-value
CV death or HHF*		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.79 (0.69-0.90)	0.001

DELIVER (dapagliflozin vs background therapy) excluding patients with previous LVEF≤40%	0.84 (0.73-0.95)	0.009
Empagliflozin vs dapagliflozin	0.94 (0.78-1.13)	0.531

Abbreviations: CI, confidence intervals; CV, cardiovascular; HHF, hospitalisation due to HF; HR, hazard ratio; LVEF, left ventricular ejection fraction.
*In DELIVER, the composite outcome includes urgent HF visits too

B.3.10 Adverse reactions

In EMPEROR-Preserved, median exposure to study medication was approximately 23 months in both treatment groups, with 84% of patients treated for at least 1 year. Safety was assessed descriptively based on AE, adverse events of special interest (AESI), and specific AE.

A similar overall proportion of patients in the empagliflozin and placebo groups reported at least one AE, most of which were of mild or moderate intensity (Table). Proportions of patients experiencing severe AE and AE leading to premature discontinuation of study medication were also similar between the two groups (Table 27).

Table 27. Overall summary of AE in the TS

Category of AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients in the TS, N (%)	2,996 (100.0)	2,989 (100.0)
Patients with any AE	2,574 (85.9)	2,585 (86.5)
Mild	724 (24.2)	686 (23.0)
Moderate	1,064 (35.5)	1,048 (35.1)
Severe	786 (26.2)	851 (28.5)
Investigator-defined drug-related AE	494 (16.5)	413 (13.8)
AE leading to discontinuation of study medication	571 (19.1)	551 (18.4)
Serious AE	1,436 (47.9)	1,543 (51.6)
Serious AE		
Resulting in death	287 (9.6)	297 (9.9)
Life threatening	127 (4.2)	114 (3.8)

Category of AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Persistent or significant disability/incapacity	53 (1.8)	43 (1.4)
Requires or prolongs hospitalisation	1,106 (36.9)	1,182 (39.5)
Congenital anomaly or birth defect	0	0
Other medically important serious event[a]	645 (21.5)	739 (24.7)

Abbreviations: AE, adverse event; TS, treated set.
Note: Percentages calculated using total number of patients per treatment as the denominator. A patient may be counted in more than one seriousness criterion.
[a]Other medically important serious event was defined as any important medical event (when based upon appropriate medical judgement) which might jeopardise the patient and might require medical or surgical intervention to prevent one of the other serious outcomes included in the definition of serious AE shown in the table above. Examples of such events could be intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of dependency or abuse.
Source: EMPEROR-Preserved CSR, Table 15.3.1.1 (166).

The overall frequency of serious AE (SAE) was lower in the empagliflozin group than in the placebo group, consistent with the efficacy analyses of AC hospitalisations (Table 28). The most frequent SAE were cardiac failure, atrial fibrillation, pneumonia and acute kidney injury. All other SAE were reported in less than 3.0% of patients per treatment group.

Table 28. Serious AE with frequency >1% -exposure adjusted, in the TS

MedDRA SoC MedDRA PT	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients	2,996 (100.0)	2,989 (100.0)
Total with SAE	1,436 (47.9)	1,543 (51.6)
Cardiac disorders	740 (24.7)	882 (29.5)
Cardiac failure	448 (15.0)	594 (19.9)
Atrial fibrillation	80 (2.7)	92 (3.1)
Cardiac failure congestive	57 (1.9)	66 (2.2)
Acute myocardial infarction	50 (1.7)	48 (1.6)
Myocardial infarction	37 (1.2)	27 (0.9)
Coronary artery disease	22 (0.7)	32 (1.1)
Infections and infestations	327 (10.9)	355 (11.9)
Pneumonia	100 (3.3)	119 (4.0)

MedDRA SoC MedDRA PT	Empagliflozin 10 mg, N (%)	Placebo, N (%)
COVID-19	49 (1.6)	47 (1.6)
Urinary tract infection	36 (1.2)	28 (0.9)
Renal and urinary disorders	165 (5.5)	200 (6.7)
Acute kidney injury	81 (2.7)	107 (3.6)
Renal impairment	38 (1.3)	42 (1.4)
Nervous system disorders	197 (6.6)	184 (6.2)
Ischaemic stroke	42 (1.4)	35 (1.2)
Neoplasms benign, malignant and unspecified	166 (5.5)	144 (4.8)
Basal cell carcinoma	17 (0.6)	32 (1.1)
Vascular disorders	130 (4.3)	154 (5.2)
Hypertensive crisis	13 (0.4)	32 (1.1)
Respiratory, thoracic and mediastinal disorders	113 (3.8)	151 (5.1)
Chronic obstructive pulmonary disease	23 (0.8)	37 (1.2)
General disorders & administration site conditions	116 (3.9)	104 (3.5)
Death[a]	56 (1.9)	38 (1.3)
With investigator-defined drug-related SAE	98 (3.3)	90 (3.0)

Abbreviations: AE, adverse event; MedDRA, Medical dictionary for regulatory activities; SoC, system organ class; MedDRA PT, Medical dictionary for regulatory activities preferred term; SAE, serious adverse event; TS, treated set.
[a]Deaths not attributed to another PT by the investigator. The frequencies of patients with fatal AE were balanced between treatment groups.
Source: EMPEROR-Preserved CSR Table 12.2:1 (166).

AESI were pre-specified in the protocol as acute renal failure, hepatic injury, decreased renal function, ketoacidosis, and AE leading to lower limb amputation. Overall frequencies of AESI were comparable in the empagliflozin and placebo groups (Table 29).

Specific AE were defined as urinary and genital tract infections, volume depletion and hypotension, hypoglycaemic events, bone fractures and urinary tract malignancies. As

known for the drug class, urinary tract infections were more common in the empagliflozin group. Uncomplicated genital tract infections also occurred more often with empagliflozin than with placebo, while complicated genital infections or those leading to treatment discontinuation had similar frequency in both groups. There was a numerical but not clinically meaningful increase in volume depletion and hypotension with empagliflozin relative to placebo, including events that were reported as SAE or that led to treatment discontinuation. No increase in confirmed hypoglycaemic events was detected for patients with or without DM, and no severe hypoglycaemic events were reported in patients without DM. The frequencies of the remaining types of specific AE were similar between the groups (Table 29).

Table 29. Summary of AESI and specific AE, TS

Category of AESI and specific AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Number of patients	2,996 (100.0)	2,989 (100.0)
AESI		
Acute renal failure	363 (12.1)	384 (12.8)
Serious	123 (4.1)	161 (5.4)
Leading to discontinuation	39 (1.3)	44 (1.5)
Hepatic injury	115 (3.8)	155 (5.2)
Serious	32 (1.1)	41 (1.4)
Leading to discontinuation	8 (0.3)	7 (0.2)
Up to 30 days after treatment discontinuation	117 (3.9)	158 (5.3)
Ketoacidosis (broad[a])	44 (1.5)	50 (1.7)
Ketoacidosis (narrow[a])	4 (0.1)	5 (0.2)
AE leading to LLA up to trial completion (investigator-defined)	16 (0.5)	23 (0.8)
Specific AE		
Urinary tract infection	297 (9.9)	243 (8.1)
Complicated	57 (1.9)	45 (1.5)
Leading to discontinuation	26 (0.9)	15 (0.5)

Category of AESI and specific AE	Empagliflozin 10 mg, N (%)	Placebo, N (%)
Genital infection	67 (2.2)	22 (0.7)
Complicated	8 (0.3)	8 (0.3)
Leading to discontinuation	11 (0.4)	2 (0.1)
Volume depletion	356 (11.9)	286 (9.6)
Hypotension (a subset of volume depletion)	311 (10.4)	257 (8.6)
Serious	62 (2.1)	47 (1.6)
Leading to discontinuation	15 (0.5)	9 (0.3)
Symptomatic hypotension (investigator-defined)	197 (6.6)	156 (5.2)
Confirmed hypoglycaemic events[b]	73 (2.4)	78 (2.6)
In patients with T1DM[c]	2/5 (40.0)	1/5 (20.0)
In patients with T2DM[c]	61/1,460 (4.2)	65/1,466 (4.4)
In patients with pre-diabetes[c]	4/1,001 (0.4)	7/979 (0.7)
In patients without diabetes or pre-diabetes[c]	6/530 (1.1)	5/539 (0.9)
Bone fracture	134 (4.5)	126 (4.2)
Serious	65 (2.2)	61 (2.0)
Leading to discontinuation	3 (0.1)	2 (0.1)
Up to trial completion	160 (5.3)	145 (4.9)
Urinary tract malignancy up to trial completion	19 (0.6)	15 (0.5)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; LLA, lower limb amputation; T2DM, type 2 DM; TS, treated set.
[a]Ketoacidosis was investigated using both broad and narrow Boehringer Ingelheim customised MedDRA queries (BIcMQs)
[b]Hypoglycaemic AE with a plasma glucose value of ≤70 mg/dL or where assistance was required
[c]Patients with events/patients in subgroup (%)
Source: EMPEROR-Preserved CSR Table 12.1.3:1 (166).

Empagliflozin vs dapagliflozin

The safety profiles of empagliflozin and dapagliflozin are considered comparable, as per clinical validation performed by the company (see section B.4.2.5). A summary of the AEs in EMPEROR-Preserved and DELIVER trials are reported below Table 30.

Due to differences in the definition of the AE included in each trial, only adverse event categories that had the same definitions are reported in the table. There are some differences in the percentages of patients that experience the AE in the empagliflozin and dapagliflozin arms; however, they are negligible and are not expected to reflect meaningful differences between the two treatment options in terms of SGLT inhibitor component but rather likely to be related to either the background therapy basket offered in each trial or the patients characteristics, e.g., comorbidities. Nevertheless, when the mean differences between the intervention and placebo in the two trials are considered, the AE incidence can be considered comparable, indicating a similar safety profile for the two drugs.

Table 30. Summary of commonly defined AE in EMPEROR-Preserved and DELIVER

	EMPEROR-Preserved			DELIVER		
AE category	Empagliflozin N= 2996 n (%)	Placebo N= 2989 n (%)	Mean difference (%)	Dapagliflozin, N=3126 n (%)	Placebo N= 3127 n (%)	Mean difference (%)
Any serious AE	1436 (47.9)	1543 (51.6)	-3.7%	1361 (43.5)	1423 (45.5)	-2%
Any AE that led to discontinuation of intervention or placebo	571 (19.1%)	551 (18.4)	0.7%	182 (5.8%)	181 (5.8)	0%
Ketoacidosis	4 (0.1%)	5 (0.2%)	-0.1%	2 (0.1%)	0 (0%)	0.1%
Cardiac failure	448 (15.0%)	594 (19.9%)	-4.9%	262 (8.4%)	343 (11.0%)	-2.6%
Atrial fibrillation	80 (2.7%)	92 (3.1%)	-0.4%	57 (1.8%)	47 (1.5%)	0.3%
Cardiac failure congestive	57 (1.9%)	66 (2.2%)	-0.3%	51 (1.6%)	73 (2.3%)	-0.7%
Acute myocardial infarction	50 (1.7%)	48 (1.6%)	0.1%	51 (1.6%)	58 (1.9%)	-0.3%

Pneumonia	100 (3.3%)	119 (4.0%)	-0.7%	97 (3.1%)	96 (3.1%)	0%
COVID-19	49 (1.6%)	47 (1.6%)	0%	165 (5.3%)	131 (4.2%)	1.1%
Urinary tract infection	36 (1.2%)	28 (0.9%)	0.3%	30 (1.0%)	32 (1.0%)	0%
Acute kidney injury	81 (2.7%)	107 (3.6%)	-0.9%	46 (1.5%)	50 (1.6%)	-0.1%
Ischaemic stroke	42 (1.4%)	35 (1.2%)	0.2%	66 (2.1%)	60 (1.9%)	0.2%
Chronic obstructive pulmonary disease	23 (0.8%)	37 (1.2%)	-0.4%	17 (0.5%)	16 (0.5%)	0%
Death	56 (1.9%)	38 (1.3%)	0.6%	36 (1.2%)	38 (1.2%)	0%

Abbreviations: AE, adverse event.

B.3.11 Conclusions about comparable health benefits and safety

There is an unmet need for licenced treatments for patients with chronic HF and mildly reduced or preserved EF, as detailed in section B.1.3.2.2. In June 2023, dapagliflozin was recommended by NICE, within its MA, as an option for treating symptomatic chronic HF with preserved or mildly reduced EF in adults (TA902) (8). Empagliflozin offers a similar mechanism of action as dapagliflozin, i.e., SGLT2 inhibition and similar clinical benefits, management and impact on HRQoL at similar costs.

Empagliflozin has demonstrated efficacy in a broad range of chronic HF patients across the full spectrum of LVEF. In the EMPEROR-Preserved trial, treatment with empagliflozin 10 mg once daily as an add-on to background therapy for symptom management in patients with chronic HF (LVEF >40%) demonstrated superiority compared to placebo plus background therapy for the primary endpoint, i.e., time to the first occurrence of adjudicated CV death or adjudicated HHF. Empagliflozin demonstrated 21% reduction in risk of CV death or HHF compared with placebo. The superiority of empagliflozin over placebo was also demonstrated for occurrence of adjudicated HHF (first and recurrent). The risk of first occurrence of AC hospitalisation was reduced in the empagliflozin group compared with the placebo group. Furthermore, fewer patients receiving empagliflozin were reported for AC or CV

mortality, although the treatment effect was not statistically significant nor was the trial powered to detect the treatment effect of empagliflozin compared to placebo for CV and AC mortality. In terms of safety, empagliflozin was well tolerated in chronic HF (LVEF >40%) patients with or without T2DM. Similarly, dapagliflozin has shown evidence of clinical efficacy over placebo for the outcomes mentioned above as indicated in the DELIVER trial and detailed in section B.2.1.

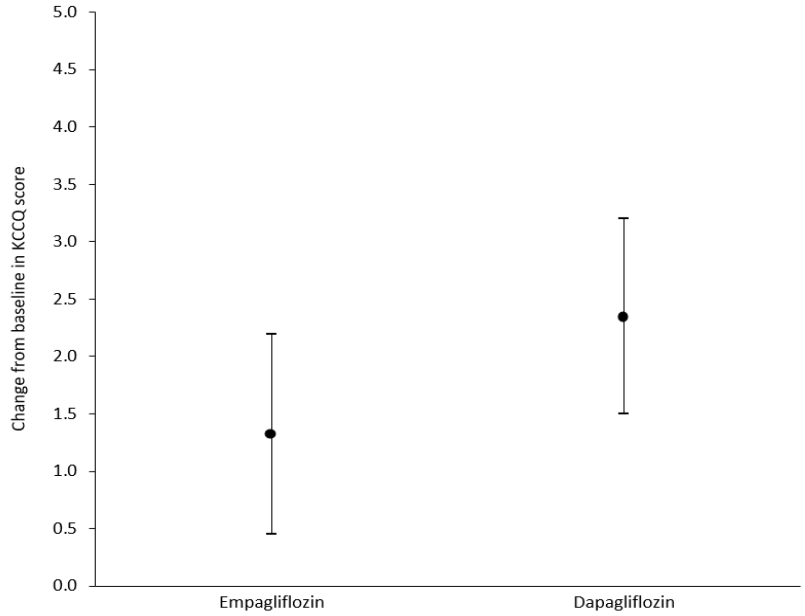
A prespecified meta-analysis of EMPEROR-Preserved and DELIVER trials was recently performed (11). The study found that empagliflozin and dapagliflozin reduced the risk of CV mortality and HHF, and therefore these two drugs offer patients with HF and LVEF >40% with treatment options, in a disease area with a historically high unmet need for licensed efficacious treatments (see section B.3.8).

Given the absence of a clinical trial including head-to-head comparison of empagliflozin and dapagliflozin, an ITC was performed to determine if the there are differences in the clinical efficacy between the two drugs. The ITC is described in section B.3.9, and the Bucher analyses showed that empagliflozin and dapagliflozin are equally effective for patients with chronic HF with preserved or mildly reduced ejection fraction.

Given the unmet need for treatments for patients with chronic HF and mildly reduced or preserved EF, empagliflozin is expected to benefit patients' HRQoL. For instance, the lower HHF rates for empagliflozin compared to placebo, but also the reductions in the risk for the composite outcome, including CV mortality or HHF, are associated with clinically meaningful improvements in HRQoL (177). Furthermore, a higher proportion of patients showed a clinically meaningful improvement in HRQoL, with KCCQ-CSS demonstrating improvement by at least five points from baseline in the empagliflozin group compared with the placebo group, after 52 weeks of treatment. The favourable effect of empagliflozin was mainly driven by the domains of symptom frequency and symptom burden, and a positive trend in favour of empagliflozin was observed in domain of physical limitations. Similarly, dapagliflozin is associated with improved HRQoL, as concluded by the NICE committee (TA902) (8). The comparable improvements in HRQoL for empagliflozin and dapagliflozin are also shown by the

mean change for baseline for KCCQ-CSS, as presented in Figure 19 below. Although there was no KCCQ-CSS data for dapagliflozin at 12 months, the improvements in mean change for both drugs is comparable, as indicated by the overlapping confidence intervals surrounding the point estimate.

Figure 19. Change from baseline to 12 months and 8 months follow-up of KCCQ-CSS for empagliflozin and dapagliflozin, respectively



Empagliflozin and dapagliflozin have also demonstrated similar safety profiles, which is based on both empirical evidence and clinical experience. AEs reported in EMPEROR-Preserved were consistent with the known safety profile of empagliflozin (see section B.3.10). Mean differences in AEs between empagliflozin and dapagliflozin vs background therapy were similar for the AEs captured having the same definitions in EMPEROR-Preserved and DELIVER trials (Table 30).

Considering the totality of evidence presented in this submission, it is reasonable to conclude that empagliflozin and dapagliflozin are comparably effective, have similar safety profiles and are associated with comparable improvements in HRQoL. Therefore, both empagliflozin and dapagliflozin offer an evidence-based treatment option on top of the background therapy for the treatment of adults with chronic HF with preserved or mildly reduced EF.

B.3.12 Ongoing studies

There are no ongoing studies of empagliflozin relevant for this appraisal.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Empagliflozin has been granted MA for the treatment of adults with chronic HF, irrespective of LVEF. As NICE TA773 recommends empagliflozin for the treatment of chronic HFrEF, this submission pertains to the remaining population with chronic HF and mildly reduced or preserved EF (LVEF >40%), which is consistent with the clinical setting described in the final scope of the decision problem for empagliflozin (178, 179). Recently, dapagliflozin is recommended by NICE in a same clinical setting as an option for treating symptomatic chronic HF. Empagliflozin is anticipated to be similarly positioned within the clinical treatment pathway as dapagliflozin, as described also in section B.1.3.2.

No differences in resource use are anticipated between empagliflozin and dapagliflozin. An important resource use for the NHS is the cost of treatment, which is identical for both treatments. That is, for both drugs, the list price of 10 mg is £36.59 per 28-tablet pack (excluding VAT) and the annual treatment cost is £477.30. It is also anticipated that that there are no differences between the two in terms of other types of healthcare resource, for instance in frequency of administration, monitoring, follow-up, and infrastructure requirements.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Based on equivalence in terms of efficacy, safety and treatment management, a descriptive cost-comparison analysis was performed to evaluate the estimated cost of empagliflozin versus dapagliflozin in the context of NHS England. As the two drugs have the same clinical efficacy (see section B.3.9), comparable safety profile (see section B.3.10), similar HRQoL (B.3.11), and the same treatment acquisition costs (see section B.4.1), economic modelling was not anticipated to provide additional evidence in this cost-comparison.

The treatment acquisition costs considered in this cost-comparison are described in Table 31. There are no differences in the treatment acquisition costs between empagliflozin and dapagliflozin.

Table 31. Acquisition costs of the intervention and comparator technologies

	Empagliflozin	Dapagliflozin
Pharmaceutical formulation	10mg oral tablet	
(Anticipated) care setting	Primary care prescription	
Acquisition cost (excluding VAT) *	List price of 10 mg is £36.59 per 28-tablet pack (excluding VAT)	
Method of administration	Oral	
Doses	10mg	
Dosing frequency	Once daily	
Dose adjustments	N/A	
Annual drug acquisition costs of treatment for a 1 year treatment duration	£477.30	
(Anticipated) average interval between courses of treatment	N/A – continuous treatment	
(Anticipated) number of repeat courses of treatment	N/A	

Abbreviations: N/A, not applicable

B.4.2.2 Intervention and comparators' healthcare resource use and associated costs

The composition and frequency of healthcare resource use and its unit costs are expected to be identical for empagliflozin and dapagliflozin based on the evidence supporting no difference in clinical outcomes or monitoring requirements between the two drugs. Both drugs have been shown to reduce the likelihood of a patient experiencing an HHF, which is a costly resource for NHS. Furthermore, since it is expected that regular monitoring for the purpose of disease management of patients with HF will take place in primary care, GP visits consist of a regularly occurring healthcare resource for empagliflozin and dapagliflozin. Finally, as CV mortality is a relevant outcome for patients with HF and LVEF>40%, its cost is also deemed important. The resource use and cost for HHF, GP visits, and CV mortality were

discussed in TA902, as described in section B.2.2 (8). In Table 32, the unit costs for HHF,GP visits, and CV mortality are presented.

Table 32. Summary of resource use and costs(8)

	Empagliflozin	Dapagliflozin
HHF (per event)		
Cost (£), price year	£2542, 2021/2022	
Source reference	Weighted average for HRG codes EB03A to EB03E	
Rationale for source	Costs reflect NHS practice, and they are weighted to represent the severity seen in NHS	
GP visits		
Cost (£), price year	£41.58, 2022	
Source reference	PSSRU	
Rationale for source	PSSRU reflects primary care costs for England	
Units per year	6	
Source reference	TA902	
CV mortality		
Cost (£), price year	£1,452, 2021/2022	
Rationale for source	Regression analysis used that predicted inpatients costs for UK cohort	
Source reference	Alva et al. (2014); TA902(8, 180)	

Abbreviations: GP, general practitioner; HHF, Hospitalisation for heart failure; HRG, healthcare resource group; PSSRU, personal social services research unit; TA, technical engagement.

B.4.2.3 Adverse reaction unit costs and resource use

Based on clinical experience and the evidence from the EMPEROR-Preserved and DELIVER trials, the safety profile is similar for empagliflozin and dapagliflozin. This is discussed in detail in section B.3.10. Therefore, there are no expected differences in healthcare resource use and hence costs of treating AEs between the two drugs.

B.4.2.4 Miscellaneous unit costs and resource use

Similar to treatment acquisition costs, healthcare resource costs, and costs for the treatment of AE, there are no anticipated differences in any other cost category between the two drugs.

B.4.2.5 Clinical expert validation

The company has performed a clinical expert validation, which includes opinion sought regarding essential aspects that are relevant to the justification for a cost comparison approach for this appraisal. Five clinical experts participated in this validation exercise to provide their opinion on the comparability of the populations of the EMPEROR-Preserved and DELIVER trials, the comparability of the endpoints included in both trials, the disease management for empagliflozin and dapagliflozin, and any potential differences in the safety profile of the two drugs.

The clinical experts agreed that the populations of the two trials are comparable and the outcomes very much aligned. Furthermore, they indicated that the disease management of the two drugs is the same, as is their safety profile. Clinical expert validation for comparability of population, outcomes, AE's and disease management between EMPEROR-Preserved and DELIVER trials is presented in Table 28 of Appendix D.

B.4.2.6 Uncertainties in the inputs and assumptions

No uncertainties are anticipated for the cost comparison inputs.

B.4.3 Base-case results

The results from the descriptive cost-comparison, as presented in section B.4.2, indicate that the total cost to the NHS is the same regardless of treatment with empagliflozin and dapagliflozin on top of background therapy for symptom management on account of equal treatment acquisition cost (section B.4.1), similar safety profiles (section B.3.10), and equal clinical efficacy for empagliflozin and dapagliflozin (section B.3.9). As shown in Table 33, the total yearly cost for the two

drugs is the same (i.e., £726.78), accounting for the yearly treatment acquisition cost, and six GP visits. When an HHF event per year is assumed, the total yearly cost is £3,268.78, same for both drugs. Finally, when the cost for CV mortality is included, the total yearly cost is £4,720.78, again same for both drugs. Based on the findings of the cost-comparison, empagliflozin offers an additional treatment option for adult patients with HF with preserved or mildly reduced EF at no additional cost to the NHS.

Table 33. Summary of relevant costs for empagliflozin and dapagliflozin

	Empagliflozin	**Dapagliflozin**
Treatment acquisition cost per year	£477.30	£477.30
GP visits, cost per year	£249.48	£249.48
Total cost per year	**726.78**	**726.78**
Incremental cost per year		**£0**
HHF cost per event	£2,542	£2,542
Total cost per year, including 1 HHF event*	**£3,268.78**	**£3,268.78**
Incremental cost per year, including 1 HHF event*		**£0**
CV mortality cost	£1,452	£1,452
Total cost per year, including CV mortality**	**£4720.78**	**£4720.78**
Incremental cost per year, including CV mortality**		**£0**

Abbreviations: CV, cardiovascular, GP, general practitioner; HHF, Hospitalisation for heart failure
* Assuming treatment acquisition cost, 6 GP visits per year, and one HHF event
** Assuming treatment acquisition cost, 6 GP visits per year, one HHF event, and CV death

B.4.4 Sensitivity and scenario analyses

No relevant sensitivity analysis was identified on the basis that the differences between dapagliflozin and empagliflozin have no impact on the clinical efficacy, safety and treatment management.

B.4.5 Subgroup analysis

In EMPEROR-Preserved, no significant variation in treatment effect was detected across pre-specified subgroups as the point estimate HR remained less than one across subgroups (Figure 18). Therefore, it is not anticipated that the technology would

differ by subgroup in the health benefits it offers and its costs versus dapagliflozin compared to the full population (see section B.3.7).

B.4.6 Interpretation and conclusions of economic evidence

Previous sections of this submission showed that empagliflozin and dapagliflozin have the similar clinical efficacy (see section B.3.9), comparable safety profile (see section B.3.10), and similar HRQoL benefits (B.3.11). Consistent with the Bucher ITC findings, a cost-comparison demonstrates that the two drugs are similar in terms of their resource use and costs to the NHS (see section B.4.1). Overall, the NHS costs associated with empagliflozin for the treatment of patients with chronic HF and mildly reduced or preserved EF are anticipated to be similar to that for dapagliflozin for this population. The above evidence suggests that empagliflozin offers an additional cost-effective treatment option for adult patients with HF with preserved or mildly reduced EF at no additional cost to the NHS. Therefore, empagliflozin should be recommended by NICE with the same positioning as for dapagliflozin, and that is, as a treatment option for all adults with chronic symptomatic HF, irrespective of EF (9).

A positive recommendation would result in the inclusion of empagliflozin in the NICE clinical guideline, NG106, as an additional treatment option for the treatment of chronic HF with LVEF >40%, a patient group with a historically high unmet need. Ensuring access to two efficacious, cost equivalent SGTL2i treatment options provides benefits to the NHS and patients including from a supply resilience perspective. The benefit of empagliflozin in reducing rates of HHF offers broader value to the NHS as avoided HHF events should free up hospital care resources and could reduce delays for some patients in need of inpatient care, which is especially important at present when the health service and workforce are experiencing significant resource constraints. Lastly, a positive recommendation for empagliflozin would ensure equal access across the UK, as empagliflozin is already approved as a treatment option for HF patients, irrespective of EF, in other parts of the UK, e.g., Scotland (181).

B.5 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]

Summary of Information for Patients (SIP)

July 2023

File name	Version	Contains confidential information	Date
ID3945_SIP July 2023	V1.0	No	13th July 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response: empagliflozin (Jardiance®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Empagliflozin is used to treat heart failure in adult patients with symptoms due to impaired heart function.(1)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: **Marketing authorisation wording:** Empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure. **Date of regulatory approval by the MHRA:** 13th June 2022 The MHRA do not publish approval notifications online. They send notifications by letter to the Marketing Authorisation Holder.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
Boehringer-Ingelheim (BI) has collaborated with Pumping Marvellous on a disease awareness campaign. BI contributed £4000 towards this campaign.

Pumping Marvellous had a couple of questions about the health-related quality of life outcomes in EMPEROR-Preserved. This was an unsolicited information request. A medical science liaison (a non-promotional staff member) responded to this enquiry.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

What is heart failure?
Heart failure is a condition that occurs when the heart cannot pump blood as well as it should; this leads to inadequate blood flow to vital organs such as the kidneys and congestion (build-up of fluid) in other vital organs such as the lungs. The term "heart failure" is misleading because the heart does not completely fail or stop beating. In some cases, heart failure can be mild and cause minor symptoms that are only evident with physical activity. Other times it can be severe (causing symptoms at rest) or even life-threatening. The most common symptoms of heart failure are shortness of breath, fatigue, leg swelling, and other signs of fluid retention.(2)

There are two main types of heart failure. They are defined based on whether the "ejection fraction" (which indicates how well the left ventricle is able to pump) is reduced or preserved:

- In "heart failure with reduced ejection fraction" (HFrEF, also called "systolic heart failure"), the heart is too weak. When the heart pumps, it doesn't squeeze normally.
- In "heart failure with preserved ejection fraction" (HFpEF, also called "diastolic heart failure"), the heart is too stiff. When the heart pumps, it doesn't relax and refill with blood normally. (2)

What does heart failure mean for my daily life?
Being diagnosed with heart failure is a significant life event and might impact how you feel. It might be associated with depression or an altered self-image. It takes time to adapt to a new way of life, new routines, to ensure that your heart failure is managed.
Rob – Heart Failure patient(3)

How many people are affected by heart failure in the UK?
Heart failure affects the lives of many people in England. More than 550,000 people in England have heart failure.(4,5)

- The prognosis for HF patients is poor.
    - There were 94,185 hospitalisations in England for heart failure in 2019/20.(6)
    - Around 24% of people diagnosed with heart failure die within the first year, with a 5-year mortality rate of 55%.(7)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

How is heart failure diagnosed?

This will depend on when you see someone due to the symptoms of heart failure that you have begun to experience such as breathlessness, tiredness, swollen ankles, or feet. Depending on how severe your symptoms are, you may feel you need to go to your hospital or your General Practice. If you present to your GP, your doctor will wish to understand your symptoms.

- Your GP will ask you detailed questions about your previous history including any heart problems in your family
- They will take your blood pressure, pulse, and a tracing of your heart (ECG)
- They will also arrange several blood tests including how effectively your kidneys and liver are working, if you are anaemic, or have a thyroid problem
- They may arrange a chest X-ray

Importantly they should perform a blood test called B-type Natriuretic Peptides or BNP. When the heart is under stress it releases a hormone, called a natriuretic peptide. If this is above normal it means, there is a possibility that you have heart failure. If this is very high your GP will refer you to hospital for an ultrasound scan of your heart (echo) to be completed within two weeks, otherwise you should have an appointment in six weeks. If you have had a previous heart attack, again the aim should be for you to be seen in two weeks. An echo will confirm a diagnosis of heart failure and the reason why you have it.

<u>Heart Failure Care in the Hospital</u>

If you have been admitted into hospital with suspected heart failure, there is evidence to suggest certain care and treatment will provide you with the best outcome. The National Heart Failure Audit in England and Wales has shown that you will do significantly better if you are given good clinical management, are under the care of a Specialist Cardiologist and are followed up by a heart failure team after you have been discharged. The aim should be that you get the right treatment, at the right time, in the right place. If you are admitted with severe symptoms, including severe breathlessness, extreme swelling, this is called acute heart failure.

<u>Tests and Investigations</u>

If it is suspected that you are in acute heart failure then you should have the specialist blood test, natriuretic peptides (as above). If this comes back raised, then you should have an ultrasound scan of your heart (echo) within 48 hours. If you are in acute failure, you should see the specialist team within 24 hours.

<u>Treatment</u>

You are likely to be offered diuretic therapy to rid the body of excess fluid that may have gathered in your lungs and other parts of the body. This is likely to be given via an injection or drip and you will be closely monitored to see how your body is coping. If you are critically unwell the team should assess you for specialist intervention therapy which may include life support machines to assist your breathing and machine support to help your kidneys to function. You will be started on treatment that is known to treat heart failure in the most effective way, including tablets such as Beta Blocker therapy, ACE inhibitors and specialist diuretics (water tablets).

Discharge Arrangements

You should not be discharged from hospital until you are stable, and you are on optimised treatment. Your wishes and those of your carers should be considered, support services in the community should have been arranged and your GP and any supportive services in the community should be aware of your treatment plan. You should be given education, support, and monitoring advice to ensure you know what to do if you experience any difficulties and who you should contact. You should also be seen by a specialist heart failure team, who are either hospital based or who sit in the community, within two weeks of leaving hospital, as early reviews reduce the chance of you being re-admitted and ensures that your long-term outcomes are better and that you can have a better quality of life.(8)

Are there any additional diagnostic tests required with the new treatment?

There are no additional diagnostic tests required to initiate Empagliflozin.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - is there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Although several therapies are recommended for the treatment of patients with chronic HF (EF ≤ 40%) (3, 20), there remains an unmet need for an effective treatment for patients with HF (EF >40%) that improves disease-related outcomes.

What do the treatment guidelines look like for chronic HF in patients with an EF >40%?

There are currently no condition-specific evidenced based treatment guidelines for chronic HF with LVEF>40%, making disease management challenging. Local clinical practice in England is informed by the NICE Guideline for chronic HF in adults (NG106).

For patients with HF with LVEF >40%, the goals of treatment are to try to keep it from getting worse (lowering the risk of death and the need for hospitalization), to ease symptoms, and to improve QoL. **(9)**
As shown in Figure 1, the NICE Guideline for chronic HF in adults (NG106) recommends the following:

- Diuretics, calcium-channel blockers, amiodarone (in consultation with a specialist) and anticoagulants are recommended for the management of all patients with chronic HF, (i.e., EF <40%, >40%)
- NG106 does not recommend any targeted pharmaceutical treatment for chronic HF (LVEF >40%). (3). For patients with chronic HF (EF >40%), treatment is focused on the management of comorbidities such as hypertension, atrial fibrillation, IHD and diabetes in line with NICE guidance.

Where should empagliflozin be used?

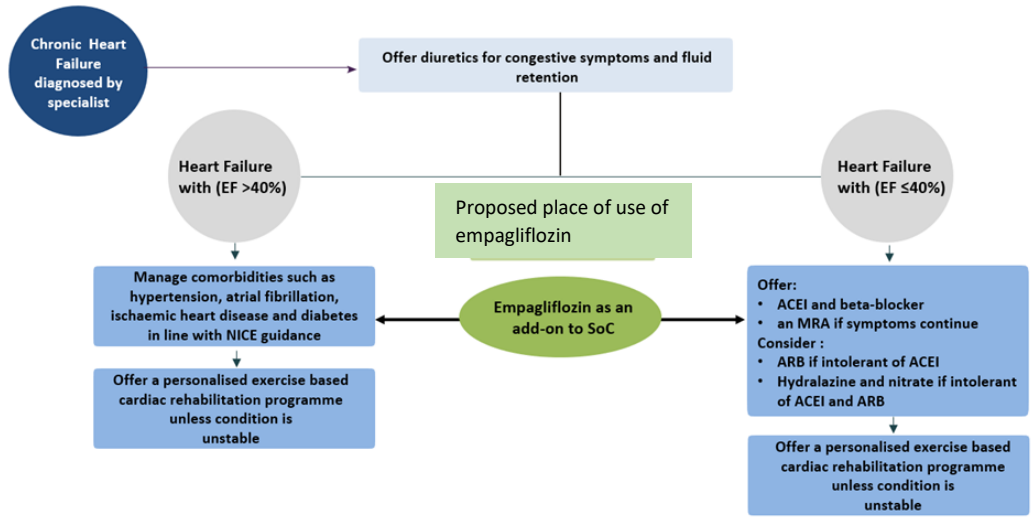
- Empagliflozin is the first therapy to demonstrate efficacy and safety in a broad range of chronic HF patients across the full spectrum of EF.(10,11) This makes it suitable for broad prescribing across primary and secondary care.
- Empagliflozin should be broadly used as an add-on to background therapy regardless of LVEF in all patients with chronic symptomatic heart failure.
- Empagliflozin is already recommended as an add-on in patients with an EF≤40%, based on EMPEROR-Reduced (TA733).
- Based on EMPEROR-Preserved, empagliflozin can also be used in patients with an EF>40% as an add-on to background therapy for the management of co-morbidities and symptomatic relief. (12)

- With broad prescribing of empagliflozin across primary and secondary care in chronic HF regardless of EF, there is an opportunity to maximise outcomes for these patients immediately, a key objective of the NHS Long Term Plan.(13)

Are there any drug-drug interactions?

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.(14)

Figure 1. Proposed use of empagliflozin within the existing NICE guidelines for the treatment of Heart Failure(15)



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

When developing this appraisal (ID3945), the Heart Failure Toolkit published by Pumping Marvellous was used understand the needs of the patients. (3,8)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Empagliflozin is an oral medication that works by inhibiting the kidney protein sodium-glucose cotransporter-2 (SGLT2) which helps sodium and glucose to be reabsorbed into the bloodstream (16). Inhibition of SGLT2 reduces blood glucose and sodium levels (which can damage blood vessels and cause high blood pressure in the long-term), and empagliflozin also has a protective effect on the heart. (17)

The exact mechanism of the heart-protective effect is not yet well defined, however SGLT2 inhibition results in increased excretion of sodium in the urine. This reduces heart muscle wall tension and oxygen demand in turn. This effect may offer significant advantage in patients with HF and may represent the mechanism contributing to the improved long-term HF outcomes with empagliflozin. (18,19)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Response: Empagliflozin is not intended to be used in combination with another medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Response: The recommended dose of empagliflozin is 10 mg once daily taken orally. No special storage conditions are required, and taking the tablet orally avoids the need for patient or clinician training as there is with treatments that are injected. (20) As empagliflozin is taken orally once daily, no significant impacts on patients and carers are expected and it should be easy to incorporate into patients' daily routines. (20)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Table 1. Overview of the studies comprising the EMPOWER clinical trial programme for empagliflozin

Study name	Study identifier	Main objective	Status	Relevant for this appraisal & reason
EMPEROR-Preserved	NCT03057951 (21)	Efficacy & safety of empagliflozin in prevention of CV death and HHF in adults with chronic HF patients (EF >40%) with or without T2DM	Completed	Yes, meets the PICO criteria as defined in the decision problem
EMPEROR-Reduced	NCT03057977 (22)	Efficacy & safety of empagliflozin in prevention of CV death and HHF in adults with chronic HFrEF with or without T2DM	Completed	No; population is not relevant for the decision problem
EMPERIAL-Preserved	NCT03448406 (23)	Effect of empagliflozin on functional ability and PROs in adults with chronic HFpEF with or without T2DM	Completed	No; primary outcome is not relevant for the decision problem; QoL secondary endpoint measured using PROs is not recommended by the NICE reference case (24)
EMPERIAL-Reduced	NCT03448419 (25)	Effect of empagliflozin on functional ability and PROs in adults with chronic HFrEF with or without T2DM	Completed	No; population is not relevant for the decision problem

EMPA-REG OUTCOME	NCT01131676 (26)	Efficacy & safety of empagliflozin in prevention of major adverse CV events, including CV death, in adults with T2DM and established CV disease	Completed	No; population is not relevant for the decision problem
EMPULSE	NCT04157751 (27)	Efficacy of empagliflozin in improving clinical and PRO outcomes in adults hospitalised for acute HF	Completed	No; population is not relevant for the decision problem
EMPA-KIDNEY	NCT03594110 (28)	Effect of empagliflozin on progression of kidney disease and the occurrence of CV death in patients with pre-existing CKD	Ongoing	No; population is not relevant for the decision problem
EMPA-VISION	NCT03332212 (29)	Effects on cardiac physiology and metabolism in patients with HF	Completed	No; the study outcomes are not relevant for the decision problem
EMPACT-MI	NCT04509674 (30)	Efficacy of empagliflozin in improving outcomes and preventing HF in adults hospitalised with an acute MI	Ongoing	No; population is not relevant for the decision problem

EMPRISE	NCT03363464 (31) EUPAS20677 (32)	Real-world comparative effectiveness, safety, healthcare resource utilisation and costs of empagliflozin *versus* DPP-4 inhibitors in T2DM in routine clinical care	Ongoing	No; population is not relevant for the decision problem

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalisation for heart failure; MI, myocardial infarction; PICO, patient intervention comparator outcome; PROs, patient-reported outcomes; T2DM, type 2 diabetes mellitus.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

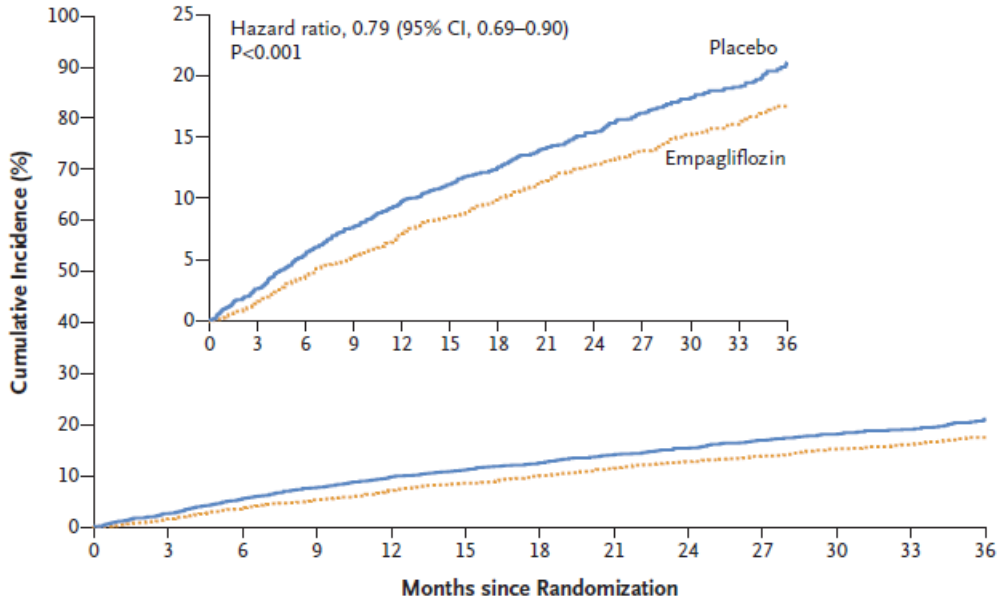
The safety and effectiveness of empagliflozin has been investigated in the EMPOWER clinical trial programme, which is the most comprehensive development programme for a SGLT2 inhibitor to date. EMPOWER comprised of 9 clinical trials and a real-world evidence (RWE) study designed to evaluate the impact of empagliflozin on cardiovascular and kidney outcomes.

EMPEROR-Preserved is a randomised, double-blind trial from the EMPOWER clinical trial programme evaluating the long-term effectiveness and safety of empagliflozin (in addition to Standard of Care [SoC] treatments) versus placebo in symptomatic chronic HF LVEF >40%. Empagliflozin reduced the combined risk of cardiovascular death or hospitalisation in patients with HF with LVEF >40%, regardless of the presence or absence of T2DM (primary endpoint in the trial), as shown in Figure 2. Empagliflozin also reduced the total number hospitalisations for heart failure (HHF) compared to SoC, which was a key secondary endpoint (Figure 3). (33)

A combined HF analysis stratified by LVEF performed on both the EMPEROR-Reduced and EMPEROR-Preserved trials (9,718 patients; 4,860 empagliflozin and 4,858 placebo) showed that empagliflozin consistently reduced the primary composite endpoint of time to CV death or first HHF for HF patients across a broad spectrum of LVEF.(11)

These data demonstrate the clinical benefit of empagliflozin regardless of EF, meaning that it can be used safely as an add-on in a primary and secondary care setting.

Figure 1. Primary outcome, a composite of CV death or HHF – *Document B, B.2.6.1, Figure 7 (page 70)*

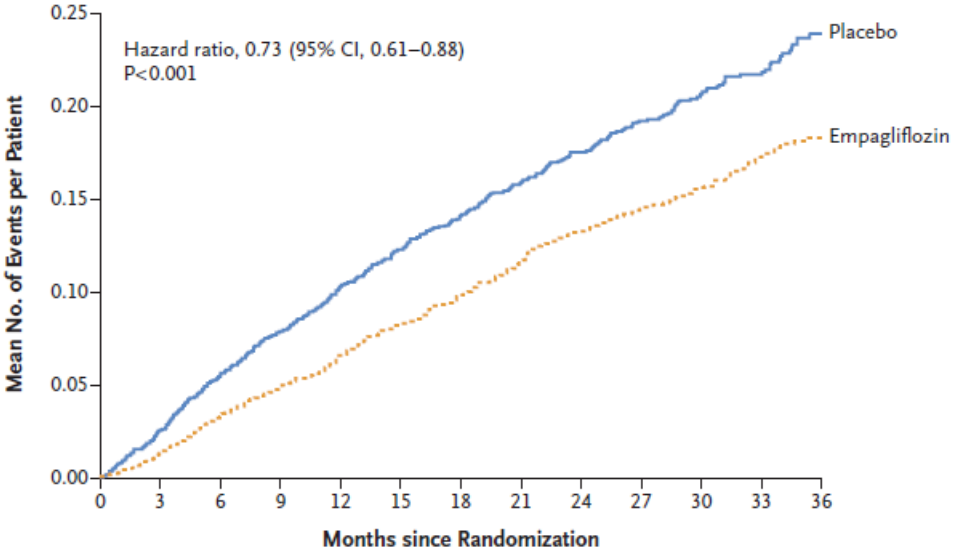


No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Abbreviation: CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis. Source: Figure 1, Anker et al 2021 (34).

Figure 2. Key secondary outcome: Total number of HHF (first and recurrent)– *Document B, Section B.2.6.2.1, Figure 8 (page 72)*



No. at Risk

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Abbreviation: HHF, hospitalisation for heart failure.
Source: Figure 3, Anker et al 2021. (34)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Patients with HF with LVEF >40% have significant impairment on their HRQoL. Improving health status and QoL is an important aspect of treatment of patients with heart failure. A significant improvement in the health status–related outcomes in chronic HF patients with LVEF >40% were observed after treating with empagliflozin and these benefits were observed early and sustained for at least 1 year.

The impact of empagliflozin on QoL was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and 12, 32, and 52 weeks. In the EMPEROR-Preserved trial, administration of empagliflozin as an add-on to SoC improved HRQoL, an effect that appeared early and was sustained for at least 1 year. Patients treated with empagliflozin had significant improvement in KCCQ-CSS versus placebo (+1.03, +1.24, and +1.50 at 12, 32, and 52 weeks, respectively; $P<0.01$). A similar improvement was also observed in KCCQ-TSS and KCCQ-OSS, as well as for the individual domains 'QoL' and 'social limitation'. There were no relevant differences between the treatment groups with regards to HRQoL as assessed by the EQ-5D-5L questionnaire. Overall, empagliflozin improved HRQoL, and the improvement was observed early and was sustained for at least one-year (11,33).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Empagliflozin is usually well-tolerated in patients with chronic HF. Common side effects include dehydration, dizziness, light-headedness, weakness, yeast infection, low blood sugar, nausea, upper respiratory tract infection, high cholesterol, joint pain, increased urination, urinary tract infection, thirst, and low blood pressure (hypotension). These are usually mild and short-lived. These can also be treated with over the counter or prescription medications after consultation with a physician (20).

Serious side effects reported with empagliflozin that may need immediate action by the emergency physician include (20):

- Ketoacidosis (increased ketones in your blood or urine)

- Sudden kidney injury
- Serious urinary tract infections (UTI)
- Dehydration (the loss of body water and salt)
- Low blood sugar (hypoglycaemia)
- Necrotizing fasciitis (a rare but serious tissue infection under the skin that can happen around the anus and genitals)
- Allergic reactions
- Increased cholesterol
- Fournier's gangrene (severe infection near the genitals)
- Angioedema (swelling under skin, typically in the eyelids, lips, hands, or feet)
- Swelling of tongue, mouth, or throat
- Trouble breathing

In the EMPEROR-Preserved trial, empagliflozin was well-tolerated in patients with chronic HF LVEF >40% with or without T2DM. The frequency of patients with least one AE, severe AEs, and AEs leading to treatment discontinuation were like placebo. The frequency of patients with serious AEs was lower in the empagliflozin group than in the placebo group, which was consistent with the efficacy analyses of all-cause hospitalisations. As known for the drug class, UTI were more common in the empagliflozin group. Uncomplicated genital tract infections also occurred more often with empagliflozin than with placebo, while complicated genital infections or those leading to treatment discontinuation had similar frequency in both groups (11,33).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety, and mode of administration
-

Response:

HF affects just under 1 million people in the UK, of which up to 50% are estimated to have chronic HF (EF >40%). (35,36) Currently ICE guideline does not recommend any specific therapy for the treatment of chronic HF (EF >40%) and the treatment focuses on the management of comorbidities.

- Empagliflozin, either alone or in combination with all appropriate therapy for HF and comorbid conditions offers to be an important advancement in the treatment of chronic HF (EF >40%): it significantly reduces the risk of CV death or HHF while significantly improving renal outcomes and QoL in a population with broad spectrum of severity of HFrEF regardless of age, gender, use of neprilysin inhibitor, presence or absence of diabetes or chronic kidney disease.(11)
- As a fixed dose, once-per-day, orally administered medication, empagliflozin is simple for physicians to initiate and for patients to adhere to, saving NHS professionals' time that would otherwise be spent on dose titration or on training patients to self-administer.
- Substantial reduction in HHF seen with empagliflozin combined with simplicity of initiation suggests that its adoption in primary care could support efficiency improvements in the allocation of NHS resources by releasing capacity in secondary care. A recently published report by NICE on implementation of NG106 noted that patients with

HF often have comorbid diabetes and CKD that require visits to additional specialist clinics.(37) SGLT2 inhibitors like empagliflozin offer an opportunity to promote a more holistic approach to treatment of adults with T2DM (37).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Empagliflozin is usually well-tolerated in patients with chronic HF.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

This submission is going through the cost comparison process, which is based on evidence that the new treatment, in this case empagliflozin, is at least as effective as a treatment that is currently recommended by NICE for the same condition, in this case dapagliflozin. The costs related to the new treatment and the already recommended treatment are compared.

The company believes that evidence shows empagliflozin to be at least as effective as dapagliflozin, with a comparable safety profile and similar benefits to patients' quality of life. The costs to the NHS are also the same, as there are no expected differences in the number of times patients will need to visit healthcare professionals whilst they are receiving treatment with empagliflozin. The costs of the treatments (price per pack) are also the same.

Therefore, empagliflozin offers an additional treatment option for patients with HF with preserved or mildly reduced ejection fraction providing patients with another choice of treatment for their condition.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative, please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Empagliflozin is a step change in the management of HF. Delivering an integrated care service is a core objective of the NHS Long Term Plan and is reflected in a recent white paper to strengthen its implementation. Further, NICE recently published a report on implementing NG106. It noted that patients with heart failure often have other co-existing conditions such as diabetes and kidney disease and may end up attending several specialist clinics.(43) SGLT2i's offer an opportunity to promote a more holistic approach to treatment of adults with T2DM and HF. Empagliflozin is already indicated for T2DM and HFrEF(20) and with data from EMPEROR-Preserved it is now licensed and has demonstrated benefit across a broad spectrum of ejection fractions. This means that all patients, regardless of ejection fraction could benefit from a targeted treatment.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

The socio-economic inequalities in CV disease present a major and persistent UK public health challenge. The UK-based population studies demonstrate that socio-economic deprivation is a strong risk factor for the development of HF and adverse HF outcomes (9, 10). Individuals in the lowest socio-economic group are 1.61 times more likely to experience incident HF than the most affluent individuals and on average, at a 3.5 years younger age with a greater comorbidity burden at the time of HF symptom onset.(36) Findings from Conrad et al. (2018) report socio-economic inequalities among all age bands and by sex in the most deprived region, which were twice as high in younger adults (IRR 2.56; 95% CI, 2.30-2.85 in the 45-54 years age group vs. 1.17; 95% CI, 1.13-1.22 in the >85 years age group).(36)

Socio-economic status has an impact on access to secondary care in the UK, and subsequently access to HF treatments. Moscelli et al. (2018) reported a statistically significant difference in waiting times across socio-economic groups for patients who attend the same hospital: patients

living in more income-deprived areas waited longer (35% difference, or 43 days) than patients who lived in areas of a lesser deprivation.(44) In addition to waiting longer, coronary heart disease patients in a lower socio-economic class were admitted to hospital less often than those in a higher class.(44) McCartney et al. (2013) reported on a prospective study of 7,049 men and 8,353 women in the west of Scotland who were followed up for 37 years; the likelihood of a hospital admission for CV disease was 21% higher for female patients in highest socio-economic class than patients in lowest class. Those patients in social class IV and V (partly skilled and unskilled occupations) also stayed 25% longer in hospital than social class I and II (professional, managerial, and technical occupations) (736 vs. 589 bed day/1,000 person-years, respectively).(45)

These studies indicate that if patients in lower socio-economic classes utilise secondary care less often, their opportunity to access HF medications would also be lower, if they are solely prescribed in secondary care.

BI support the UK Government's and NICE's commitment to the reduction of health inequalities, reiterated in the recent NICE five-year strategy publication.(46,47) Principle 9 of NICE's Social Value Judgments states that due regard must be given to reducing inequalities. It states that equality should be considered in relation to the nine protected characteristics in the Equality Act 2010 (age, disability, gender reassignment, race, religion or belief, sex, sexual orientation, marriage and civil partnership, pregnancy and maternity) and socio-demographic factors.(47,48) Further, the COVID-19 Marmot review aims to reduce the widened gap in health inequalities and build a fairer society post pandemic.(49) Broad prescribing of SGLT2i across primary and secondary care can support the reduction in disparity in terms of access to HF care across socio-economic groups within the UK. Together with TA773, this appraisal further supports this objective by providing a treatment option for those patients regardless of EF.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/

- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

ICER: Incremental cost effectiveness ratio
KCCQ: Kansas City Cardiomyopathy Questionnaire
QALY: Quality Adjusted Life Year
SoC: Standard of Care

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	British Society for Heart Failure
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? Yes • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? Yes • Other (please specify):
5. Brief description of the organisation (including who funds it).	British Society for Heart Failure (BSH) is a charitable membership organisation for healthcare professionals. It was founded in 1998 and set up as a charitable company in 1999. Its aims are to increase knowledge and promote research surrounding heart failure with the intention of delaying or preventing the onset of heart failure and improving patient care and also to provide expert advice to healthcare professionals, patients or other organisations such as the NHS when appropriate. In order to support its work, a membership fee is charged to individuals who join BSH but the main funding comes from holding educational heart failure related events and activities which attracts sponsorship and grants from a variety of supporters with an interest in this field. BSH receives a relatively low level of donations at this point and does not receive any government funding.

6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Boehringer Ingelheim Limited: £60,000 – Exhibition package (including a Symposia) at BSH's annual conference £20,500 – QI Academy project sponsorship £20,000 – Sponsorship of PEF webinar £20,000 – Grant toward heart failure Mapping Project £20,000 – Sponsorship of BSH's Pathway Project £10,000 – Contribution to BSH's partnership scheme £9,000 – Exhibition package at BSH's annual multi-disciplinary training event Astra Zeneca: £93,490 - Exhibition package (including a Symposia and workshop) at BSH's annual conference £100,000 – Grant towards BSH's 25:25 and Fast Track Cities heart failure project £15,000 – Contribution to BSH's partnership scheme £9,000 – Exhibition package at BSH's annual multi-disciplinary training event
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	Empagliflozin is an sglt2 inhibitor like the comparator, dapagliflozin, and several meta-analyses support a class effect for the two SGLT2is. Both empagliflozin and dapagliflozin reversibly inhibit the sodium-glucose co-transporter 2 (SGLT2) receptor in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion. Both are sglt2 inhibitors with high sglt2/sglt1 selectivity. The mechanism of action for reducing heart failure risk is incompletely understood and a several mechanisms may be involved including diuretic and anthypertensive effects, weight loss and improved glycaemic control, improved myocardial energetics and improved endothelial function.
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	For empagliflozin, the primary endpoint in the EMPEROR-Preserved trial (cardiovascular death or hospitalisation for HF) was reduced by 21% in the treatment group and for dapagliflozin, the primary end point in the DELIVER trial (worsening heart failure or cardiovascular death) was reduced by 18% in the treatment group. The metaanalysis by Vaduganathan (Lancet 2022. 400;757-67) showed that in the two relevant randomised trials the SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73–0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for heart failure (0·74 [0·67–0·83]). The TA committee have already stated in the earlier appraisal that they were satisfied that like dapagliflozin, empagliflozin significantly reduced the combined risk of cardiovascular death or first heart failure event in HFpEF and HFmrEF.
10. What impact would the technology have on the current pathway of care?	Two are some practical issues should be taken not account. Heart failure patients have multiple comorbidities, and over 40% of HFpEF patients have type 2 diabetes. For these patients, empagliflozin may be preferred by the GP as a dose increase to 25mg can be employed (under the T2DM indication) for improved gycaemic control. Separately, heart failure services across the country are working at capacity. Many patients with type 2 diabetes or CKD with proteinuria indications are already prescribed empagliflozin. NICE Chronic Heart Failure Guidelines (NG106, 2018) recommend that for a different HF medicine class, beta-blockers (BB), that all patients are switched over onto a BB licensed for heart failure. If empagliflozin is approved by NICE then heart failure teams will not feel the need to switch these patients onto dapagliflozin, avoiding extra work without patient benefit due to the similar clinical effectiveness.

11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Empagliflozin would be used in both primary and secondary care, and commenced on the advice of a heart failure specialist.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	No.
14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Empagliflozin is expected to offer similar health benefits to dapagliflozin.
15. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	Empagliflozin reduces heart failure admissions and readmissions. Around 70% of the cost of heart failure care in England is due to hospital admissions. Heart failure is the commonest cause for admission in over 65-year-olds and admission rates are increasing as the population ages with a one third increase in England in 5 years. Reducing hospital admissions will reduce the overall cost of care but also has a wider impact on secondary care as bed capacity in England is limited and emergency departments are over-stretched. Reducing this demand for the commonest admitted condition for older patients will aid wider NHS services.
17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	No.

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BMJ TAG

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

Cost-Comparison Appraisal

Source of funding

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence and validation of clinical analyses; cross checking of company's search strategies; and drafted the summary, background and clinical sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

EAG	External Assessment Group
AC	All-cause
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
AFl	Atrial flutter
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
CC	Cost-comparison
CCA	Cost-comparison appraisal
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Controlled Register of Trials
CHF	Chronic heart failure
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTR	Clinical trial report
CV	Cardiovascular
DM	Diabetes mellitus
EAG	External Assessment Group
ECG	Electrocardiogram
ED	Emergency department
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
ER	Emergency room
ESC	European Society of Cardiology
FAS	Full analysis set
GP	General practitioner
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalisation for heart failure

HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire - Total Symptom Score
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire - Overall Summary Score
LA	Left atrial
LOS	Length of stay
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
MeSH	Medical Subject Headings
MRA	Mineralocorticoid receptor antagonist
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network-meta-analysis
NR	Not reported
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OC-AD	Observed case including data after treatment discontinuation as well as on-treatment data
OC-OT	Observed case including on-treatment data only
OR	Odds ratio
RCT	Randomised controlled trial
RS	Randomised set
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SGLT	Sodium-glucose co-transporter
SGLT1	Sodium-glucose co-transporter- 1
SGLT2	Sodium-glucose co-transporter- 2
SLR	Systematic literature review

SmPC	Summary of medicinal product characteristics
STA	Single technology appraisal
T2DM	Type 2 diabetes mellitus
TA	Technology appraisal
TS	Treated set
UHFV	Urgent heart failure visit
UK	United Kingdom
USA	United States of America

1 Summary of EAG's view of the company's CCE case

A cost-comparison model was developed by the company which assessed empagliflozin compared to dapagliflozin in chronic heart failure (CHF) with preserved or mildly reduced (>40%) left ventricular ejection fraction (LVEF; HFpEF/HFmrEF); dapagliflozin is an intervention recently recommended for this indication in TA902.[1] This cost comparison appraisal (CCA) covers part of the company's marketing authorisation in CHF (specifically the group with LVEF >40%) but the EAG notes that it has already been recommended by the National Institute for Health and Care Excellence (NICE) for use in those with CHF and reduced LVEF (HFrEF; LVEF ≤40%).[2, 3] Dapagliflozin also has marketing authorisation for both of these populations and has already been recommended by NICE in both indications.[1, 4, 5]

The External Assessment Group (EAG) notes that empagliflozin and dapagliflozin have the same mechanism of action and are used at the same dose, frequency and both are oral tablets. Based on their experience of empagliflozin and dapagliflozin in HFrEF, where both are already recommended by NICE,[3, 5] the EAG's clinical experts consider there to be no appreciable difference between them in terms of efficacy or safety and would not expect this to differ for the HFpEF/HFmrEF population.

The company puts forward a case of clinical similarity between empagliflozin and dapagliflozin in this indication. Given no randomised controlled trials (RCTs) directly comparing empagliflozin and dapagliflozin in this population are available, indirect treatment comparisons (ITCs) were required. The company performed ITCs performed for various outcomes via Bucher analyses, with EMPEROR-Preserved and DELIVER trials included in these analyses.[6, 7] The EAG considers these trials to match the population in the NICE final scope and decision problem well.[8]

While some differences in trial baseline characteristics were noted, the EAG's clinical experts did not consider these differences were substantial enough to impact outcomes for empagliflozin or dapagliflozin. Similarly, while definitions of outcomes compared in ITCs differed, the EAG was able to explore the impact of these on ITC results using additional publications. All outcomes used in the economic model for TA902 are covered in this report.[1] The EAG was able to perform additional ITCs to provide formal comparisons for Kansas City Cardiomyopathy Questionnaire (KCCQ) outcomes and to explore uncertainty related to the inclusion of the group with prior LVEF ≤40% in DELIVER, which was not included in EMPEROR-Preserved and was the most notable difference between the two trials.

The EAG considers that the analyses performed by the company and the EAG represent a robust assessment and support the clinical similarity between empagliflozin and dapagliflozin. While having direct evidence from an RCT comparing the two would be preferable, the EAG considers that the assessment in this report is a robust alternative given this is not available. There are no major concerns about the methodology used or differences between trials, and differences in outcome definitions have been explored. While the EAG notes there may be a trend for increased non-cardiovascular (CV) mortality for empagliflozin compared to placebo (but a reduction in CV mortality), the EAG is unable to explain this finding and notes that it may be observed in DELIVER as well but to a lesser extent; it does not consider this to be an issue that would prevent a CCA being appropriate but considers it worthy of note.

Considering the company and EAG analyses, as well as feedback from clinical experts and knowledge of the similarity between the drugs in terms of mechanism and dose, the EAG concludes that it is likely empagliflozin is similar to dapagliflozin in terms of outcomes assessed in this report, including hospitalisation for heart failure, CV mortality, all-cause mortality, KCCQ outcomes and adverse events. While these conclusions are not without uncertainty based on the 95% confidence intervals obtained from ITCs, and that a lack of statistically significant differences does not necessarily confirm there is no difference, the EAG is reassured based on feedback from clinical experts that there is no appreciable difference between them in clinical practice when used for HFrEF. Therefore, the EAG considers that the CCA approach is appropriate in this case.

Finally, the EAG agrees with the company's conclusion that empagliflozin and dapagliflozin generate similar costs to the NHS.

2 Background

The description of the disease area and treatment pathway (Section B.1.3 of the company submission [CS]) of this cost-comparison appraisal (CCA) submission is largely the same as that described in the single technology appraisal (STA) submission to the National Institute for Health and Care Excellence (NICE) in 2022 (Draft Guidance published in February 2023),[9] with the exception that dapagliflozin is now mentioned as a treatment in the pathway given its recent recommendation for chronic heart failure (CHF) with preserved or mildly reduced left ventricular ejection fraction (LVEF; HFpEF or HFmrEF) as part of TA902.[1] The External Assessment Group (EAG)'s clinical experts at the time of the STA submission considered the company's description to be an accurate overview. The only substantial addition since then is mention of dapagliflozin as a treatment option for this population.

The mechanism of action of empagliflozin (Jardiance®) is described in Section B.1.2 of the CS; it is an oral, reversible and selective inhibitor of sodium-glucose co-transporter (SGLT) 2 and is to be taken at a dose of 10 mg once daily. The EAG notes that this is the same mechanism and dose as described for dapagliflozin (Forxiga®), as detailed in TA902 and its Summary of Product Characteristics.[1, 4] Empagliflozin is already recommended by NICE for the treatment of the following indications, as is dapagliflozin:

- as part of combination treatment for type 2 diabetes mellitus (T2DM; TA336);[10]
- as a monotherapy for treating T2DM (TA390);[11]
- and for treating CHF with reduced LVEF (≤40%; HFrEF; TA773).[3]

Empagliflozin is being considered in a CCA for this indication as it was considered plausible that it may have similar efficacy and safety to dapagliflozin, which has recently been recommended for use in this same indication.[1] In addition, the EAG notes that the mechanism of action and dosing the same as that described for dapagliflozin in this indication. The EAG's conclusion regarding the appropriateness of a CCA for this treatment and indication is summarised in Section 1 of this report and discussed in more detail throughout.

3 Critique of the decision problem in the company's submission

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE) in Section B.1.1 of the company submission (CS),[8] together with the rationale for any deviation from the final scope (Table 2 of the CS). The company highlights that the decision problem addressed is in line with the NICE final scope for all parameters. Comments from the External Assessment Group (EAG) are provided in the subsections that follow; overall, the EAG considers the decision problem addressed and the evidence used to address it to be reasonable and the EAG has performed additional analyses where they were deemed useful, for example to better align outcome definitions across trials.

3.1 Population

The population covered by the company is in line with the NICE final scope. The CS describes those with chronic heart failure (CHF) with preserved or mildly reduced left ventricular ejection fraction (LVEF; HFpEF or HFmrEF) as the focus of this cost-comparison appraisal (CCA), which is defined as a LVEF >40% in the CS and is in keeping with the European Society of Cardiology (ESC) guidelines.[12] While empagliflozin has marketing authorisation for all symptomatic CHF,[2] it has already been recommended by NICE for CHF with reduced LVEF (HFrEF; LVEF ≤40%),[3] meaning the current appraisal covers the remaining population in the marketing authorisation for CHF. This is the same population that NICE recommendations for dapagliflozin (the comparator of interest for this appraisal as described in Section 3.3) cover, as it is recommended for HFrEF and HFpEF/HFmrEF populations in TA679 and TA902, respectively.[1, 5]

EMPEROR-Preserved is the trial used in the CS to inform outcomes for empagliflozin.[13] The trial population matches that outlined in the decision problem well; it includes adults with CHF with New York Heart Association (NYHA) class II-IV and an LVEF >40% diagnosed for at least 3 months prior to screening, with or without diabetes mellitus (DM). More detailed inclusion and exclusion criteria are described in Table 11 of the CS and Table 12 of this report. At the time of the single technology appraisal (STA) submission, the EAG's clinical experts considered EMPEROR-Preserved to be a reasonable representation of HFpEF/HFmrEF patients in UK clinical practice but noted that the age may be younger than expected (mean 72 years, while patients are more often in their 80s in their clinical experience). Other differences compared to UK clinical practice were mentioned and discussed in the EAG's critique of the STA submission,[9] but none of these, including age, were thought to be a major concern in terms of potential impact on results of the trial.

The EAG notes that EMPEROR-Preserved excluded patients that had any prior recording of LVEF ≤40% (Section 9.3.2 of the clinical trial report [CTR]);[6] this is a key difference to the comparator trial (DELIVER) included for dapagliflozin (see Sections 4.3.1, 4.3.2 and 4.4.3 for further discussion),[7] which the committee in TA902 concluded was broadly generalisable to UK clinical practice.[1] Other differences between EMPEROR-Preserved and DELIVER are discussed in Sections 4.3.1, 4.3.2 and Appendix 9.3. In general, the EAG's clinical experts were not concerned that these differences would have a large impact on outcomes but noted that the difference between prior LVEF ≤40% inclusion and the proportion using loop diuretics might have some impact.

Indirect treatment comparisons (ITCs) were performed via Bucher analyses[14] within the overall population of EMPEROR-Preserved (Section 4.3) rather than a specific subgroup, which the EAG considers to be appropriate and in line with the decision problem and NICE final scope.[8]

3.2 Intervention

The EAG notes that the intervention focused on in the CS matches the NICE final scope and that the EMPEROR-Preserved trial uses the empagliflozin dose outlined for CHF in its marketing authorisation (oral tablet, 10 mg once daily).[2, 6, 8]

Empagliflozin is to be used in combination with standard care (including loop diuretics and symptomatic treatments for comorbidities; Table 2 of the CS). At the time of the STA submission,[9] the EAG's clinical experts considered the standard care treatments used in EMPEROR-Preserved to be a reasonable representation of those used in UK clinical practice. Some potential differences compared to UK practice were noted in terms of proportions, but they were considered to be in keeping with the comorbidities reported for those included in the trial and not a major concern. They noted that ~2% of patients in each group were treated with angiotensin receptor-neprilysin inhibitor (ARNI), which would not be used in HFpEF/HFmrEF patients in the UK as no ARNI holds UK marketing authorisation for this indication, but may be because it is used for HFmrEF patients in the USA.[6]

One of the EAG's clinical experts noted that fewer patients are receiving loop diuretics (67.7% in both arms of EMPEROR-Preserved) than would be expected and that patients not taking these are more likely not to have genuine heart failure. They indicated that this might reduce the efficacy of empagliflozin slightly, particularly when compared to DELIVER as proportions are slightly higher in that trial, but that any impact on comparisons between empagliflozin and dapagliflozin would likely be small (see Appendix 9.3).[6, 7]

3.3 Comparators

Empagliflozin is compared to dapagliflozin in this CCA. Given the lack of trials comparing these two treatments directly, ITCs have been performed using the Bucher method (Section 4.3).[14] The EAG considers this comparison to be appropriate; while only recently recommended for this HFpEF/HFmrEF,[1] the only other options for this group are standard of care treatments and the EAG anticipates that dapagliflozin would eventually be used in a large proportion of those eligible. While established clinical management (i.e. standard of care) without empagliflozin is also listed in the NICE final scope as a comparator of interest, the EAG considers dapagliflozin to be the most appropriate comparator for this CCA as dapagliflozin represents an add-on treatment to standard of care and it is likely that it would be used where standard care is deemed insufficient.

The dose for dapagliflozin specified in its marketing authorisation for CHF is used in the DELIVER trial (oral tablet, 10 mg once daily).[4, 7] The DELIVER trial is similar to the EMPEROR-Preserved trial in terms of population, standard of care used and outcomes assessed and the EAG considers it to be a reasonable source of data for dapagliflozin in HFpEF/HFmrEF. Some differences are however noted and discussed in Sections 4.3.1, 4.3.2 and Appendix 9.3. In the STA for dapagliflozin in this indication, despite some potential differences, the EAG's clinical experts considered it to be a reasonable reflection of the population in UK practice, and the committee also came to this conclusion.[1]

3.4 Outcomes and subgroups

The outcomes presented in the CS match those in the final scope well; all outcomes are covered in the EMPEROR-Preserved trial.[6] The EAG considers that ITCs between empagliflozin and dapagliflozin have been performed by the company for most of the important outcomes (primary composite outcome of hospitalisation for heart failure [HHF] or cardiovascular [CV] mortality, and HHF, CV mortality and all-cause mortality as individual outcomes); however, the EAG also considered it feasible to perform ITCs for Kansas City Cardiomyopathy Questionnaire (KCCQ) outcomes and has performed these additional analyses (see Sections 4.3 and 4.4.2). ITCs were not performed for adverse events and rates in intervention and placebo arms were instead compared between the two studies, which the EAG considers to be reasonable (see Sections 4.3.1 and 4.3.3.3). This covers all outcomes that were important in the STA for dapagliflozin in this indication.[1]

Definitions used for outcomes in EMPEROR-Preserved are considered to be reasonable; however, the EAG has a preference for alternative definitions/analyses for some outcomes included in the ITCs vs dapagliflozin given they better match the definitions from the DELIVER trial (see Sections 4.3.2

and 4.4). Median length of follow-up in EMPEROR-Preserved and DELIVER was similar (26.2 months vs 27.6 months).[6, 7]

Various subgroup results for the EMPEROR-Preserved trial are presented in the CS (Section B.3.7) but ITCs vs dapagliflozin are focused on the overall trial population. The EAG agrees with this given it reflects the population for which dapagliflozin has recently been recommended in HFpEF/HFmrEF.[1] The company has, however, explored the impact of not including the group with prior LVEF ≤40% from DELIVER in the ITC (based on results from a secondary publication for DELIVER). The EAG considers this to be a useful additional analysis and has expanded this to additional outcomes, but notes that there are further limitations when this subgroup is used for DELIVER (see Section 4.4.3).

3.5 Other relevant factors

The company mentions in the CS that broad prescribing of SGLT inhibitors such as empagliflozin and dapagliflozin in primary and secondary care could reduce the inequality in terms of accessing HF care in the UK (Table 2 of the CS). It describes socio-economic inequalities in CV disease, where socio-economic deprivation is, *"a strong risk factor for the development of heart failure (HF) and adverse HF outcomes"*.[15, 16] The company states that making empagliflozin available as an additional SGLT2 treatment option would, *"offer patients an additional choice and also provide further reassurance as they would not have to reply on only one recommended treatment option"*. Evidence for a link between socio-economic status and access to secondary care (and subsequently access to HF treatments) is discussed by the company; waiting times were significantly different across socio-economic groups for patients attending the same hospital in the publication cited by the company and differences in the proportion of CV disease patients admitted to hospital were also noted.[17, 18] The company states that if treatments such as empagliflozin are solely prescribed in secondary care, this could lead to an equality issue related to socio-economic status.

The EAG acknowledges the company's points above but notes that as part of the STA submission for empagliflozin in this indication,[19] the committee discussed these arguments and concluded that empagliflozin, if recommended for this indication, *"would be started on the advice of a heart failure specialist who can determine the most appropriate treatment"*.

The EAG notes that there is no Patient Access Scheme available for empagliflozin, which is also the case for dapagliflozin.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company describes the methods used to perform the clinical systematic literature review (SLR) in Appendix D.1 of the company submission (CS). This was used to identify trials for inclusion in the indirect treatment comparisons (ITCs) detailed in Section 4.3. It was performed according to a pre-agreed protocol and in accordance with the Cochrane Handbook and the Centre for Reviews and Dissemination (CRD). The most recent updates to searches were performed in January 2023. The searches for the SLR were much broader than the scope of this cost-comparison appraisal (CCA) in terms of interventions and comparators and covers empagliflozin and dapagliflozin outlined in the decision problem (Section 3).

The External Assessment Group (EAG)'s critique of the SLR methods are presented in Section 9.2. It concludes that methodology used in the SLR process is reasonable and that it is unlikely that relevant trials of empagliflozin or dapagliflozin in chronic heart failure (CHF) with preserved or mildly reduced (>40%) left ventricular ejection fraction (LVEF; HFpEF/HFmrEF) have been missed. While two other empagliflozin studies may provide data for HFpEF/HFmrEF (EMPERIAL-Preserved and EMPA-VISION),[20, 21] the focus of these studies was on functional outcomes such as exercise capacity, with the only relevant outcome being Kansas City Cardiomyopathy Questionnaire (KCCQ) scores but at a much shorter time period (12 weeks) compared to EMPEROR-Preserved (8 months).

4.2 Critique of trials of empagliflozin and comparator interventions

4.2.1 Trials included and quality assessment

One randomised controlled trial (RCT) comparing empagliflozin (oral tablet 10 mg once daily) vs placebo (both in addition to standard of care treatments) was used in the CS to provide data for the efficacy and safety of empagliflozin for treating HFpEF/HFmrEF. This was a phase III double-blind RCT, with further study details described in Table 12 of Appendix 9.3. As discussed in Section 4.1, the EAG agrees that this is the only relevant RCT available for empagliflozin in this indication. As part of the single technology appraisal (STA) that was performed for empagliflozin in this indication, the EAG's clinical experts considered EMPEROR-Preserved to be a reasonable reflection of the HFpEF/HFmrEF population in UK clinical practice (Section 3.1). This RCT covers the outcomes listed in the National Institute for Health and Care Excellence (NICE) final scope and those included in the

economic model for TA902 (Section 3.4),[1, 8] where dapagliflozin was recently recommended for this indication (despite some differences in outcome definitions or analysis methods between trials; see Sections 4.3.1, 4.3.2 and Appendix 9.3).

Data from EMPEROR-Preserved were used in the CS to perform ITCs (via Bucher analysis) against data from DELIVER, a dapagliflozin RCT in the same indication (Section 4.3). The similarity of EMPEROR-Preserved and DELIVER is discussed in Section 4.3 and Appendix 9.3, and results of ITCs performed by the company and any additional analyses performed by the EAG are discussed in Section 4.3.3 and 4.4. As noted in Section 4.1, the EAG also considers that DELIVER is the only relevant RCT available for dapagliflozin in this indication.

Quality assessment performed by the company for EMPEROR-Preserved and DELIVER is presented in Table 27 of Appendix D of the CS. The company's critique suggests a low risk of bias for both trials with no major issues identified for either trial. The EAG performed its own critique of these two trials, which is presented in Appendix 9.1; while the EAG considers there to be some concerns for both trials about the appropriateness of a missing at random assumption for survivors with missing KCCQ data (and the exclusion of KCCQ data that was collected following the date the COVID-19 pandemic was declared in DELIVER), it considers the two trials to be similar in terms of quality. There are no major concerns about the quality of either of these two trials.

4.2.2 Results from EMPEROR-Preserved

4.2.2.1 HHF and mortality outcomes

Efficacy results for EMPEROR-Preserved are provided by the company in Section B.3.6 of the CS. In summary, empagliflozin improved various outcomes compared to placebo; statistically significant reductions in the risk of composite outcome (cardiovascular [CV] death or first hospitalisation for heart failure [HHF]) and first HHF as a standalone outcome were identified. The point estimate for CV mortality as an individual end-point also suggested a benefit of empagliflozin (although this was not statistically significant) while the point estimate of 1.00 for all-cause (AC) mortality suggests no difference between empagliflozin and placebo groups. Hazard ratios (HRs) for these outcomes, as reported in the CS, are summarised in Table 1 below. Other outcomes were also reported to be improved by empagliflozin (e.g. renal function, onset of diabetes mellitus and AC hospitalisation) but the EAG does not focus on these given they were not included in the economic model for

dapagliflozin in TA902.[1] The EAG discusses KCCQ results and adverse events (AEs) in the sections that follow.

Table 1. Clinical results from EMPEROR-Preserved – empagliflozin vs placebo (both in addition to standard of care treatments)

Outcome	HR (95% CI)	p-value
CV mortality or HHF	0.79 (0.69 to 0.90)	<0.001
HHF	0.71 (0.60 to 0.83)	<0.0001
CV mortality	0.91 (0.76 to 1.09)	0.300
AC mortality	1.00 (0.87 to 1.15)	0.989

These are results according to the original analyses for each outcome in EMPEROR-Preserved, based on data in Section B.3.6 of the CS.

Abbreviations: AC, all-cause; CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio.

The EAG notes that while results for CV mortality and AC mortality were both non-significant, the point estimate for CV mortality suggests a benefit of empagliflozin vs placebo but for AC mortality the value of 1.00 suggests equivalence. If these were considered to be true reflections of the impact of empagliflozin on these outcomes compared to placebo, this may indicate that, at least in this trial, non-CV deaths occurred more often in the empagliflozin group compared to placebo. The EAG confirmed this from figures presented in the Clinical Trial Report (CTR) for EMPEROR-Preserved; while empagliflozin appears to [redacted] CV death from [redacted] (Figure 1), there appears to be a [redacted] on non-CV death, which starts [redacted] (Figure 2). The proportion of patients with non-CV death events was [redacted] for empagliflozin and [redacted] for placebo.

The EAG notes that this [redacted] to have been the case in the EMPEROR-Reduced trial for those with CHF and reduced LVEF (≤40%; HFrEF) or for DAPA-HF, which was a trial of dapagliflozin in HFrEF (HR point estimates for CV mortality and AC mortality were similar for both outcomes and suggest a benefit for empagliflozin or dapagliflozin).[22, 23] There may be some signal from DELIVER that non-CV deaths are also increased in the dapagliflozin group compared to placebo in the HFpEF/HFmrEF population (as the point estimate of the HR for AC mortality is closer to 1.0 than the point estimate of the HR for CV mortality; 0.94 vs 0.88) but this is slightly less notable than the difference for EMPEROR-Preserved (1.00 vs 0.91).

The EAG is unable to explain why this may be occurring but notes that it may be something specific to the HFpEF/HFmrEF population and more visible in the EMPEROR-Preserved trial due to unknown

factors or chance. The EAG's clinical experts were also unaware of a biological rationale that could explain this and indicated that it may be due to chance, given the trials were not powered to assess mortality outcomes alone, although one clinical expert suggested that it may be because the HFpEF/HFmrEF population generally has more comorbidities compared to HFrEF and may die for non-CV reasons even if a CV death is prevented. In conclusion, the EAG considers this important to note but considers it to be an unresolvable issue based on the data currently available. The EAG does not consider it to be a major issue at this point in time given that it may be an effect also seen in DELIVER (to a lesser extent) and because the differences for CV or AC mortality vs placebo are non-significant. While it is possible that it is just a chance find, the EAG cannot be sure that this is the case.

Figure 1. Time to adjudicated CV death (considering non-CV death as a competing risk) – reproduced from Figure 11.1.2.4.2: 1 of the CTR for EMPEROR-Preserved

Abbreviations: CTR, clinical trial report; CV, cardiovascular; Empa, empagliflozin.

Figure 2. Time to non-CV death – reproduced from Figure 15.2.4.19: 1 of the CTR for EMPEROR-Preserved

Abbreviations: CTR, clinical trial report; CV, cardiovascular; Empa, empagliflozin.

4.2.2.2 Quality of life – KCCQ

The KCCQ - Clinical Summary Score (KCCQ-CSS) was measured as a secondary endpoint of EMPEROR-Preserved to assess quality of life (see Table 2 for more details on the primary analysis of this outcome). Results for other subscores of KCCQ were also presented by the company in Table 22 of the CS. Results were reported as mean change from baseline scores at 52 weeks. The results indicate that empagliflozin led to statistically significant improvements in KCCQ subscores (including KCCQ-CSS, Total Symptom Score [KCCQ-TSS] and Overall Summary Score [KCCQ-OSS]) vs placebo at this time-point. However, the EAG notes that differences may not be clinically important, as a threshold of ≥5 points has been suggested as indicating clinically important changes from baseline (and differences vs placebo did not reach this).[24] Based on responder analysis data included for EMPEROR-Preserved by the EAG in Section 4.4.2, benefits vs placebo in terms of the proportion with ≥5-point improvement or deterioration on KCCQ-CSS and KCCQ-TSS scores were also observed for empagliflozin. However, these were not all statistically significant based on 95% confidence intervals (CIs) crossing 1.0. The company also notes in Section B.3.6.2.9 that no differences between

treatment groups were observed when assessed by the EQ-5D-5L questionnaire in EMPEROR-Preserved.

4.2.2.3 Adverse events

Median study medication exposure in EMPEROR-Preserved was ~23 months in both treatment groups (84% of patients were treated for ≥1 year). The company summarises AEs in Section B.3.10 of the CS (Tables 27-29 of the CS). The results indicate that the numbers of serious adverse events (SAEs) were similar between groups and the most frequent were cardiac failure, atrial fibrillation, pneumonia and acute kidney injury. All other SAE were reported in fewer than 3.0% of participants per treatment group. AEs leading to discontinuation of study medication occurred in 19.1% and 18.4% of empagliflozin and placebo groups, respectively. The EAG considers the AE rates to be similar between groups and is not concerned that empagliflozin is likely to increase the risk of any substantially.

4.2.2.4 Subgroups

As discussed in Section 3.4, ITCs in Section 4.3 were performed in the overall EMPEROR-Preserved population and analyses in subgroups were not performed, which the EAG considers to be appropriate. However, the CS (Section B.3.7) describes various subgroup analyses for the primary composite outcome (CV death or HHF). The EAG notes that while there may be some variation in point estimates for some analyses (e.g. higher baseline LVEF categories have point estimates closer to 1.00), there are no significant differences identified and all point estimates are consistent with a benefit of empagliflozin over placebo. The EAG reviewed subgroup analyses for some other outcomes of interest to this appraisal (first HHF and CV mortality as standalone outcomes) in the CTR of EMPEROR-Preserved and are satisfied that there are no major concerns for these outcomes; the most notable difference was between [redacted]); however, the EAG acknowledges that the NYHA class III/IV group is [redacted] NYHA class I/II and that these subgroup analyses were considered exploratory and did not account for multiple testing. The EAG has no reason to believe that the impact of empagliflozin on any particular subgroups for certain outcomes would differ to that of dapagliflozin.

Further subgroup results of interest have been presented by the company in Appendix E of the CS; the most notable difference here is for CV mortality in those aged ≥70 years vs <70 years (HR 0.85 [95% CI 0.68 to 1.06] vs 1.03 [95% CI 0.74 to 1.43]), with point estimates suggesting a benefit of empagliflozin in the ≥70 group but slightly more events in the <70 group compared to placebo. However, the EAG notes the limitations of these subgroup analyses and that 95% CIs for both cross 1.00.

Given that dapagliflozin in TA902 was not limited to a subgroup of the trial,[1] the EAG considers it appropriate that ITCs in this appraisal focus on the whole EMPEROR-Preserved population and do not have major concerns about any of the variation reported for subgroups within this trial.

4.3 Summary and critique of the indirect treatment comparison

4.3.1 Methods and approach

In the absence of direct evidence comparing empagliflozin with dapagliflozin, outlined as the comparator of interest in the decision problem (Section 3.3), ITCs were performed for mortality and HHF-related outcomes using the two key RCTs (EMPEROR-Preserved and DELIVER) for these interventions vs placebo (Section B.3.9 of the CS).[6, 7] In addition, visual comparisons for other outcomes (AEs and KCCQ score) between the trials were made by the company but not via formal ITCs (Sections B.3.10 and B.3.11 of the CS).

Analyses were based on full trial populations rather than specific subgroups within trials, which the EAG considers to be reasonable (Section 3.1). For outcomes formally compared using ITCs (HHF, CV mortality, AC mortality and composite of HHF and CV mortality), the Bucher method was used by the company.[14] These four outcomes were selected for formal ITCs given they were the primary composite outcomes in the two trials or key secondary outcomes where benefits for empagliflozin and dapagliflozin have been observed in this population. This was performed by the company using Microsoft® Excel, as described by Tobias *et al.* 2014.[25] As described in Section B.3.9 of the CS, the company considered a Bucher analysis to be the most appropriate method for comparing empagliflozin and dapagliflozin following a feasibility assessment because:

- Only two trials were identified for the ITCs, meaning a network meta-analysis is not possible;
- Study designs for EMPEROR-Preserved and DELIVER RCTs are very similar, with a similar sample size and a similar target population recruited:

- the main difference is noted to be the inclusion of 18% of patients in DELIVER with a prior LVEF ≤40%, which was an exclusion criterion in EMPEROR-Preserved – given the committee concluded that the DELIVER population was generalisable to UK practice when this population is included in TA902,[1] the company do not consider it to be a major issues in terms of these ITCs);
- Baseline characteristics were deemed to be similar between the two trials by the company, including use of background treatments that made up standard of care in each trial;
- No meaningful differences in placebo + background treatment group outcomes were noted by the company for the four outcomes analysed using ITCs;
- A difference in terms of the definition of the primary composite outcome between trials was noted (i.e. DELIVER included urgent heart failure visits [UHFV] as well as HHF) but given UHFV events were rare and point estimates of HRs for dapagliflozin vs placebo for HHF and UHFV individually were very similar (0.77 and 0.76, respectively), the company concluded this is not likely to affect conclusions;
- Other outcomes (HHF, CV mortality and AC mortality) were reported by both trials, meaning they could be compared via ITCs;

- It was concluded that a matching-adjusted indirect comparison (MAIC) would *"add little to no additional value"* as no clinically meaningful differences between baseline characteristics of the two trials were considered to be present and any differences would not be expected to influence the results; the company highlights that a MAIC would still not resolve differences that have been identified, such as between prior LVEF ≤40% inclusion in the two trials or the definitions used for the composite primary outcome. It also notes that a MAIC would increase uncertainty given a smaller effective sample size would be generated after the matching procedure.

EAG comment

Overall, the EAG agrees with the company's conclusion that the EMPEROR-Preserved and DELIVER RCTs are broadly similar in terms of study design and population (see Sections 4.3.2 and Appendix 9.3) and that Bucher ITCs are an appropriate method of comparing outcomes between these two trials.

As noted in Section 4.3.2 and Appendix 9.3, clinical experts advising the EAG were not concerned that any differences in baseline characteristics between trials would have a large impact on the efficacy of empagliflozin or dapagliflozin. In addition, the EAG notes that the potential impact of the most notable difference between trials (the inclusion or exclusion of those with prior LVEF ≤40%) on ITCs has been explored (see Section 4.4.3).

The EAG notes that, in addition to the difference in composite outcome definition between trials highlighted by the company, other slight differences exist for other outcomes (see Section 4.3.2). However, as described in Section 4.4, the company and/or the EAG has explored these (other than HHF as data was not available) using additional published data, and the EAG does not consider them to impact conclusions.

While the EAG acknowledges that the company has compared KCCQ outcome data between the two trials, it notes that this was not via a formal ITC and results are visually compared in Figure 19 of the CS. The EAG considers it possible and useful to perform a formal ITC via the Bucher method for this outcome, given KCCQ score informed the economic model in TA902,[1] and discusses this further in Sections 4.3.3.2 and 4.4.2.

The EAG considers the company's comparison of AEs, which was not via formal ITCs and involved visually comparing intervention and placebo rates between the two trials, to be reasonable. While this included discontinuations that were related to AEs, it did not include AC discontinuations and the EAG has included a comparison of this in Section 4.3.3.3. The EAG considers all outcomes commented on in Sections B.3.9 to B.3.11 of the CS to be relevant and has covered them in the sections that follow. It also considers that all outcomes relevant to the TA902 appraisal,[1] where dapagliflozin was recommended for HFpEF/HFmrEF, have been covered in this report.

The EAG agrees with the company that the placebo rates for the four outcomes analysed by ITCs (Table 24 of the CS) are similar overall; while the placebo + standard of care rates for the composite outcome, HHF and AC mortality were higher in DELIVER compared to EMPEROR-Preserved (and very similar for CV mortality), these were small differences of 1 to 3% and would be expected to also apply to the intervention arms. The EAG's clinical experts did not consider there to be any important differences between trials with regards to standard of care treatments used (see Section 4.3.2 and Appendix 9.3).

While the company states that performing MAICs could not resolve the issue with regards to inclusion or exclusion of patients with prior LVEF ≤40% in the two trials, the EAG considers it would be possible to perform MAICs adjusting the EMPEROR-Preserved population to match the subgroup within DELIVER that did not have prior LVEF ≤40%, as baseline characteristics and outcomes for this subgroup are reported in a secondary publication of DELIVER.[26] However, as discussed in Section 4.4.3, the EAG does not consider MAICs using this subgroup from DELIVER to be a priority given it would still be associated with the limitations resulting from potential imbalances between dapagliflozin and placebo arms within DELIVER. The EAG prefers analyses based on the full trials of EMPEROR-Preserved and DELIVER, and considers any analyses using the DELIVER subgroup to be exploratory only.

While the EAG agrees that Bucher analyses are reasonable in this case, it notes that the company's statement about increased uncertainty if a MAIC was used (due to reduced effective sample size as a result of matching) is not relevant; if there were differences between the two trials that were concerning, a method that involves adjustment for these differences (such as a MAIC) should be the preferred option regardless of the impact it would have on effective sample size and precision, and reduced precision should not be used as a reason not to adjust for potentially clinically important differences between trials. The EAG's opinion in this case is that it is satisfied that Bucher analyses are a reasonable approach to ITCs; while a MAIC would have the advantage of reducing any differences that are present between the trials, it is a method that interferes with or breaks randomisation and should only be used if there are differences in treatment effect modifiers between trials included in ITCs that are expected to confound results. As the EAG is satisfied that differences between trials in this CCA should not have a large impact on the results of the ITCs (Section 4.3.2 and Appendix 9.3), or subsequent conclusions, it considers that a MAIC would not provide any advantages over Bucher analyses currently performed.

4.3.2 Included studies

Two placebo-controlled RCTs were included in the comparisons performed between empagliflozin and dapagliflozin (EMPEROR-Preserved and DELIVER).[6, 7] See Section 4.1 for a discussion of the SLR used to identify studies for inclusion in ITCs. As noted in Section 4.3.1, the company considers these trials to be very similar in terms of baseline characteristics, use of standard care treatments and study design.

With regards to baseline characteristics, overall, the EAG concludes that while some differences in baseline characteristics and use of standard of care treatments are noted between the two trials, clinical expert feedback to the EAG was that these differences are small and unlikely to have a large impact on the relative treatment efficacy of either empagliflozin or dapagliflozin. In addition, the EAG notes that characteristics are well-balanced in both of the trials. Based on this, the EAG is satisfied that there are no large differences in baseline characteristics that necessitates other methods for ITCs, such as MAICs. The EAG summarises these characteristics in Table 11 of Appendix 9.3 and provides a more detailed discussed there of any differences noted.

Both of the EAG's clinical experts noted that the biggest difference between the two trials concerns the inclusion or exclusion of those with a prior LVEF ≤40%, with one noting that they would expect outcomes to be slightly better in the group that have had a prior measurement ≤40%; if true, this would mean that ITCs including full populations from both trials may favour dapagliflozin slightly. This has been explored by the company and/or the EAG in Section 4.4.3.

The EAG considers the trial design to be very similar in the two studies and considers the main difference to be the inclusion/exclusion of those with prior LVEF ≤40%, as already mentioned above. While other slight differences are noted (such as age, time since diagnosis of CHF required and N-terminal pro-B-type natriuretic peptide [NT-proBNP] threshold for those with atrial fibrillation or flutter), the EAG does not consider these to be major issues based on feedback from the EAG's clinical experts that there are no important differences in baseline characteristics between the trials. The EAG notes that the same analysis sets were used for time-to-event outcomes (intention to treat; ITT) and AEs (ITT patients with at least one treatment of intervention or placebo) in the two studies, but the primary analysis set for KCCQ outcomes was different. The EAG explored the impact of KCCQ analyses that were more aligned between studies in Sections 4.3.3.2 and 4.4.2. Differences in study design between the trials are summarised in Table 12 of Appendix 9.3.

The company noted the difference between trials with regards to the composite outcome definition; however, the EAG identified another difference in terms of the HHF outcome as used in the company's analyses. For KCCQ outcomes, the EAG notes that while DELIVER originally focused on the TSS subdomain of KCCQ (as opposed to EMPEROR-Preserved which focused on CSS),[6, 7] published data are available for KCCQ-CSS in DELIVER which is what was presented in the CS for this CCA.[27] However, the time-points used to assess KCCQ-CSS differ between the two trials for those presented in the CS. Other outcomes were considered to be similar in terms of definitions between the two

trials and definitions for all outcomes considered in this CCA are summarised below in Table 2. Most differences between outcome definitions have been explored by the company and/or the EAG in Sections 4.3.3 and 4.4.

Table 2. Comparison of outcome definitions and analysis methods between EMPEROR-Preserved and DELIVER[a]

Outcome	EMPEROR-Preserved	DELIVER	EAG comment
Primary composite outcome – HHF or CV mortality	Time to first HHF or CV death. See individual components in subsequent rows for definitions.	Time to first worsening HF event (HHF or UHFV) or CV death. See individual components in subsequent rows for definitions.	EMPEROR-Preserved included only HHF whereas DELIVER included HHF or UHFV events in addition to CV death. The company explained that the HR for UHFV in DELIVER is very similar to that for HHF (0.76 vs 0.77) and, given it is a rare outcome, would be unlikely to impact estimates obtained for empagliflozin vs dapagliflozin in terms of the primary composite outcome. The EAG identified a paper where outcome definitions for EMPEROR-Preserved were aligned (including for the difference in UHFV inclusion for the composite outcome) with those in DELIVER and explored this in Section 4.4.1.[28]
HHF	*HHF event required all of the following to be met:* • admission to hospital with primary diagnosis of HF; • LOS at least 12 h (or change of calendar date if times unavailable) or an ER visit for ≥12 h if IV therapy received; • exhibits documented new or worsening symptoms[b] due to HF on presentation; • objective evidence of new or worsening HF, including at least two physical examination	*HHF event required all of the following to be met:* • admission to hospital with primary diagnosis of HF; • LOS at least 24 h (or change of calendar date if times unavailable); • exhibits documented new or worsening symptoms[b] due to HF on presentation; • objective evidence of new or worsening HF, including at least two physical examination findings or one physical examination finding and at least one laboratory criterion[c];	A difference in the LOS required to be considered HHF is noted – with a duration of 12 h vs 24 h required in EMPEROR-Preserved vs DELIVER. The EAG considers that if anything, this difference may bias against empagliflozin as it is easier to reach a ≥12 h duration; it may be easier to reduce the number of hospitalisations ≥24 h (DELIVER) than those ≥12 h (EMPEROR-Preserved) relative to placebo. The EAG identified a paper

	findings or one physical examination finding and at least one laboratory criterion[c]; • and patient received initiation or intensification of at least one treatment specifically for HF[d].	• and patient received initiation or intensification of at least one treatment specifically for HF[d].	where outcome definitions for EMPEROR-Preserved were aligned with those in DELIVER; however, this did not include data for the HHF outcome separately. The EAG has commented on this in Section 4.4.1.[28]
UHFV	NA	*UHFV event required all of the following to be met:* • Urgent, unscheduled office/practice or ED visit for primary diagnosis of HF, but not meeting criteria for HHF; • Meets all signs and symptoms described for HHF above, including symptoms and physical examination/laboratory findings; • and received at least one treatment specifically for HF[e];	UHFV was not reported in the CS for EMPEROR-Preserved but the EAG identified a paper that aligned outcome definitions for EMPEROR-Preserved with DELIVER, which appeared to include UHFV events.[28] Given UHFV was not ultimately included in the economic model in TA902,[1] the EAG has not focused on UHFV as an outcome, but it has explored the results in this additional paper in Section 4.4.1 with regards to the primary composite outcome.
CV mortality	CV death includes death classified in any of the following categories: • due to acute myocardial infarction; • sudden cardiac death; • due to heart failure; • due to stroke; • due to CV procedures; • due to CV haemorrhage; • due to other CV cause; • undetermined cause of death.	CV death includes death classified in any of the following categories: • due to acute myocardial infarction; • sudden cardiac death; • due to heart failure; • due to stroke; • due to CV procedures; • due to CV haemorrhage; • due to other CV cause.	The two studies differed with regards to whether deaths of undetermined cause were considered CV events or not. The EAG identified a paper where outcome definitions for EMPEROR-Preserved were aligned with those in DELIVER and has explored this in Section 4.4.1.[28]

	As noted in the list above, deaths of undetermined cause were classed as CV death in EMPEROR-Preserved.	See supplementary material 3 associated with the primary DELIVER publication for detailed definitions of each of these events (pages 15-16).[7] Deaths of unknown/undetermined cause were not classed as CV deaths in DELIVER.	
AC mortality	Deaths due to any cause.	Deaths due to any cause.	Given the objective nature of this outcome, the definitions are considered to be identical.
KCCQ	Data for KCCQ-CSS are presented in the CS, at a time-point of 12 months (Figure 19 of the CS). Results are presented for the change from baseline in intervention vs placebo. This was the primary KCCQ outcome predefined in the EMPEROR-Preserved trial. The primary analysis for KCCQ outcomes was in the treated set (those randomised and receiving at least one dose of intervention or placebo) and used on-treatment values only (OC-OT analysis); analysis in ITT set (all of those randomised regardless of whether any treatment received) and including on and off-treatment values was also available (OC-AD analysis). It also included imputation of a score of 0.0 for those that died.	Data for KCCQ-CSS are presented in the CS, at a time-point of 8 months (Figure 19 of the CS). Results are presented for the change from baseline in intervention vs placebo. KCCQ-TSS was the primary KCCQ outcome predefined in the DELIVER trial, but KCCQ-CSS data have been published and used by the company in this CCA.[27] Primary analysis of KCCQ outcomes was performed using the ITT set (all randomised regardless of whether any treatment received), including all data irrespective of whether patient has discontinued treatment. It only included data for those surviving at this time-point. Analyses from DELIVER also only included patients that had their 8-month assessment done prior to the COVID-19 pandemic was declared (defined as 11th March 2020), which was not mentioned for EMPEROR-Preserved.	Analysis of KCCQ outcomes differed between trials in terms of time-point (12 vs 8 months), data included (treated with only on-treatment values used vs randomised with all data used) and inclusion of patients that had died (included with a score of 0.0 imputed or not included). The EAG identified data within the EMPEROR-Preserved CTR that allows KCCQ outcomes to be more aligned with regards to these factors and explored the impact of this in Sections 4.3.3.2 and 4.4.2.[6] The EAG notes that the difference in terms of excluding post-COVID-19 8-month assessments may represent a bias in favour of dapagliflozin. The EAG also explored the difference between empagliflozin and dapagliflozin in terms of proportions achieving a certain level of improvement or deterioration compared to baseline, as

			mean change from baseline scores may be limited in terms of identifying important differences (Section 4.4.2).

[a]Data taken from the CS, CTR and secondary publications for EMPEROR-Preserved, and publications and associated supplementary material for DELIVER.[6, 7, 27, 28]; [b]at least one of dyspnoea, reduced exercise tolerance, fatigue or other symptoms of worsened end-organ perfusion or volume overload; [c]physical examination findings considered to be due to HF included peripheral oedema, increasing abdominal distention and ascites (in the absence of primary hepatic disease), pulmonary rales/crackles/crepitations, increased jugular venous pressure and/or hepatojugular reflux, S3 gallop and clinically significant or rapid weight gain thought to be related to fluid retention. Laboratory evidence of new or worsening HF was to be obtained within 24 h of presentation and included increased BNP/NT-proBNP concentrations consistent with decompensation of HF, radiological evidence of pulmonary congestion, non-invasive diagnosis evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output and invasive diagnostic evidence with right heart catheterisation showing a pulmonary capillary wedge pressure ≥18 mmHg, central venous pressure ≥12 mmHg or a cardiac index <2.2 L/min/m^2; [d]including at least one of augmentation in oral diuretic therapy (if intensification is solely oral diuretics, the duration of hospitalisation must be at least 24 h for EMPEROR-Preserved), initiation of IV diuretic or vasoactive agent, or mechanical or surgical intervention (including mechanical circulatory support and mechanical fluid removal); [e]initiation of IV diuretic or vasoactive agent (augmentation of oral diuretic therapy not sufficient to fulfil UHFV criteria) or mechanical or surgical intervention, including mechanical circulatory support or mechanical fluid removal.

Abbreviations: AC, all-cause; BNP, B-type natriuretic peptide; CCA, cost-comparison appraisal; CS, company submission; CTR, clinical trial report; CV, cardiovascular; EAG, External Assessment Group; ED, emergency department; ER, emergency room; HF, heart failure; HHF, hospitalisation for heart failure; HR, hazard ratio; ITT, intention to treat; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; LOS, length of stay; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OC-AD, observed case including data after treatment discontinuation as well as on-treatment data; OC-OT, observed case including on-treatment data only; UHFV, urgent heart failure visit.

4.3.3 Results of the company's analyses

4.3.3.1 Primary composite outcome (CV mortality or HHF), HHF and mortality outcomes

The company presents an overview of results from their Bucher analyses of four outcomes alongside HRs taken from EMPEROR-Preserved and DELIVER trials in Table 25 of the CS, which is reproduced below in Table 3. As concluded by the company, no statistically significant differences between empagliflozin and dapagliflozin were identified; the point estimates for two outcomes (primary composite and HHF as its own outcome) suggest slightly better results for empagliflozin, while the opposite is observed for CV and AC mortality outcomes.

While the HR point estimates suggest slight differences favouring one of the two treatments, the EAG considers that these are small differences, with values all close to 1.00. There is also uncertainty in the results based on 95% CIs, which range from a potential benefit of empagliflozin to a potential benefit of dapagliflozin for all outcomes; the EAG considers that if there are likely to be only very slight differences between two treatments and they may potentially be equivalent; only a very large trial would obtain estimates with CIs that do not cross 1.00. Based on these results and the fact that no statistically significant differences have been identified (and as the two trials are fairly large with ~3000 patients per arm in each), the EAG considers that outcomes with empagliflozin are likely to be similar to those with dapagliflozin in the HFpEF/HFmrEF population, although it acknowledges that uncertainty remains based on 95% CIs.

When the EAG's preferred analyses for the composite outcome and CV mortality are considered (where outcome definitions are better aligned), the EAG considers the results to further support similar effectiveness (Section 4.4.1). While definitions for the HHF outcome differed between the two trials (12 h vs 24 h hospitalisation), better aligned data were not available for this outcome; the EAG considers that this difference is unlikely to change results for this outcome (as explained in Section 4.4.1). The EAG also applied its preferred data from EMPEROR-Preserved to a scenario, where DELIVER trial data excluding those with prior LVEF ≤40% is included (Section 4.4.3). Excluding this subgroup is more favourable for empagliflozin for all four outcomes (although there remains slightly more AC deaths for empagliflozin compared to dapagliflozin); however, the EAG notes that these DELIVER subgroup analyses have limitations and should be considered exploratory (Section 4.4.3).

The EAG's clinical experts also noted that in their experience of treating patients with HFrEF, there is no appreciable difference between empagliflozin and dapagliflozin in terms of outcomes and they would not expect this to differ when the HFpEF/HFmrEF population is considered. They also consider the evidence available across the CHF spectrum to support the equivalence of the two treatments.[29]

Table 3. Overview of the results of the company's Bucher analyses – adapted from Table 25 of the CS

Analysis	HR (95% CI)	p-value
CV mortality or HHF[a]		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.79 (0.69 to 0.90)	<0.001
DELIVER (dapagliflozin vs background therapy)	0.82 (0.73 to 0.92)	<0.001
Empagliflozin vs dapagliflozin	*0.96 (0.81 to 1.15)*	*0.691*
HHF[b]		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.71 (0.60 to 0.83)	<0.001
DELIVER (dapagliflozin vs background therapy)	0.77 (0.67 to 0.89)	<0.001
Empagliflozin vs dapagliflozin	*0.92 (0.74 to 1.14)*	*0.470*
CV mortality[c]		
EMPEROR-Preserved (empagliflozin vs background therapy)	0.91 (0.76 to 1.09)	0.310
DELIVER (dapagliflozin vs background therapy)	0.88 (0.74 to 1.05)	0.1678
Empagliflozin vs dapagliflozin	*1.03 (0.80 to 1.33)*	*0.806*
AC mortality		
EMPEROR-Preserved (empagliflozin vs background therapy)	1.00 (0.87 to 1.15)	1.000
DELIVER (dapagliflozin vs background therapy)	0.94 (0.83 to 1.07)	0.3425
Empagliflozin vs dapagliflozin	*1.06 (0.88 to 1.28)*	*0.531*

[a]The EAG notes that the trials differed with regards to duration of HHF required, inclusion of UHFV events and inclusion of undetermined deaths as CV deaths; [b]the EAG notes that the trials differed with regards to duration of HHF required; [c]the EAG notes that the trials differed with regards to whether deaths of undetermined cause were included as CV deaths.

The EAG has explored the differences noted in footnotes a and c in Section 4.4.1. An analysis exploring the difference in footnote b could not be performed as data was not available for HHF in EMPEROR-Preserved aligned to DELIVER, but the EAG has commented on this in Section 4.4.1. See Table 2 for more detail on these differences.

Abbreviations: AC, all-cause; CI, confidence interval; CS, company submission; CV, cardiovascular; EAG, External Assessment Group; HHF, hospitalisation for heart failure; UHFV, urgent heart failure visit.

4.3.3.2 KCCQ outcomes

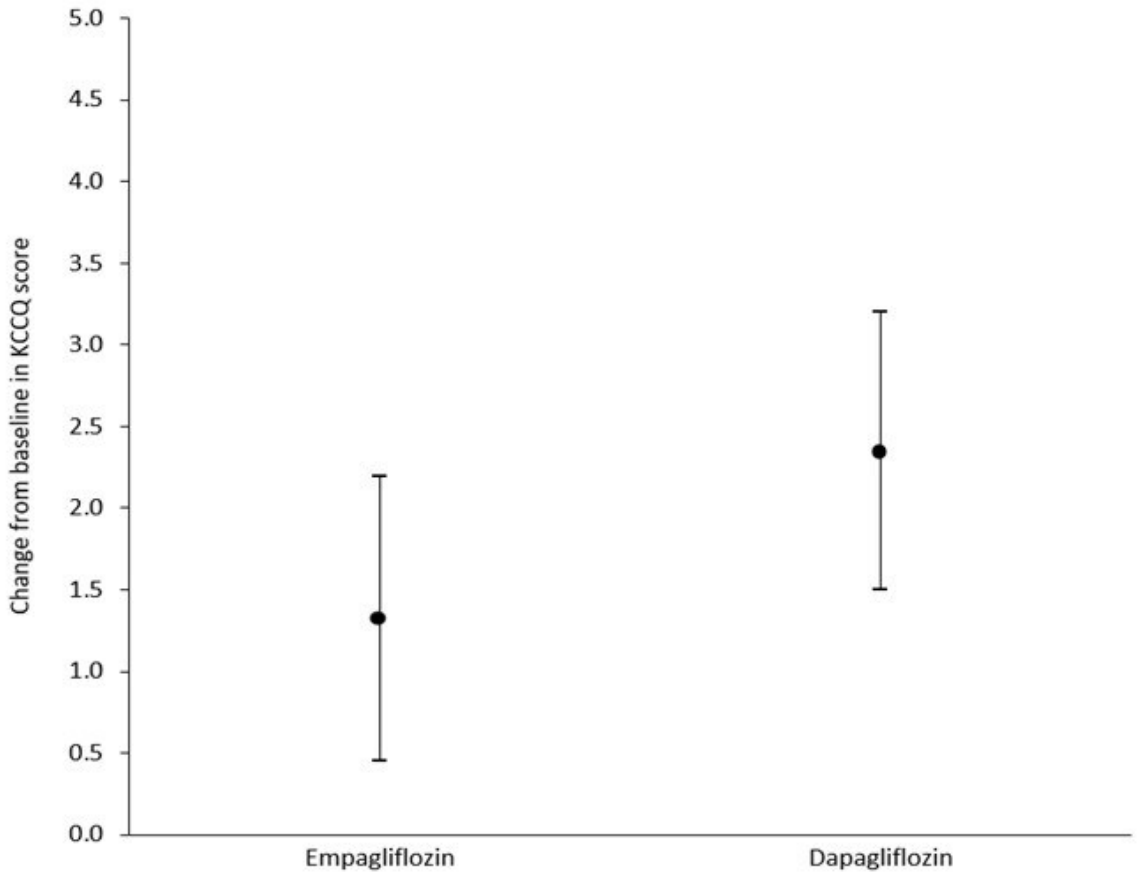
The company did not perform a formal ITC for KCCQ outcomes in the two trials and instead briefly commented on differences displayed in Figure 19 of the CS (Figure 3 below). It notes that

improvements in change from baseline scores for KCCQ-CSS are comparable for empagliflozin and dapagliflozin given that the point estimates overlap. While not clear in the CS, the EAG considers the results presented in this figure are relative effects of each treatment vs placebo, as the points on the graph appear to match values of 1.32 for empagliflozin (Table 22 of the CS) and 2.30 for dapagliflozin (central illustration of a secondary publication of DELIVER).[27] The EAG notes that differences in this outcome in terms of time-point and data analysed exist (see Table 2). The EAG located the 8-month data for EMPEROR-Preserved using a definition that was considered to be more in line with DELIVER (using all randomised patients, including on- and off-treatment values and not imputing a score of 0.0 for those that had died) in the CTR and notes that the value is [redacted] compared to that reported in the CS ([redacted]; Table 15.2.3.6:5 of the CTR).[6]

The EAG notes that results for both definitions mentioned above for empagliflozin are lower compared to results obtained for dapagliflozin (suggesting less of a benefit in terms of KCCQ score for empagliflozin). However, overall, the EAG considers that differences for both drugs vs placebo could be considered similar as they are both below the threshold usually considered to be a clinically important change for KCCQ outcomes (5-points, as mentioned in the EAG reports of the STAs for empagliflozin and dapagliflozin in this indication), which may suggest that neither of the treatments have a large impact on KCCQ score at the trial-level.[1, 9] The EAG notes that the analysis in DELIVER only included patients that had their 8-month assessment prior to the date the COVID-19 pandemic was declared, which might bias slightly against empagliflozin in any comparisons given this was not mentioned for analyses from EMPEROR-Preserved. This is not something that could be resolved in any of the analyses performed by the EAG in Section 4.4.2.

Given that KCCQ scores were used in the economic model in TA902, the EAG consider it appropriate to perform formal ITCs for this outcome and have performed these via Bucher analyses in Section 4.4.2. These analyses prioritise data that is better aligned in terms of time-point and data analysed, given the differences highlighted in Table 2, and are presented for KCCQ-CSS and KCCQ-TSS given KCCQ-TSS was the subscore focused on in DELIVER. In addition, given that it may be more difficult to identify differences in mean change from baseline scores compared to individual differences at a patient level, the EAG has also performed Bucher analyses for the proportions with ≥5-point improvements or deteriorations from baseline in Section 4.4.2, as data were identified for both studies in this format.[27, 30] The EAG considers that the results of these additional analyses are in line with KCCQ outcomes being similar for empagliflozin and dapagliflozin in this indication (Section 4.4.2), although uncertainty remains based on 95% CIs.

Figure 3. Change from baseline relative to placebo at 12 months (EMPEROR-Preserved) and 8 months (DELIVER) follow-up for KCCQ-CSS – reproduced from Figure 19 of the CS



Abbreviations: CS, company submission; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score.

4.3.3.3 Adverse events

The company did not perform ITCs for AEs and instead compared intervention and placebo rates between studies (Table 13 in Appendix 9.4), concluding that the safety profiles of empagliflozin and dapagliflozin are comparable. In addition to the AE rates reported, the company cites clinical validation by five experts confirming that they considered the safety profile of the two drugs to be similar in clinical practice (Table 28 of Appendix D of the CS). While some differences in the proportions in the empagliflozin arm of EMPEROR-Preserved compared to dapagliflozin in DELIVER are noted, the company concludes that these are likely to be trial-specific factors given placebo rates are similar to intervention rates in each trial, meaning differences between the relative treatment effects (vs placebo) of empagliflozin and dapagliflozin are very small.

The EAG has added some additional events to Table 13 in Appendix 9.4, even if definitions are not identical in the two trials, as they are noted as AEs of special interest (AESI) in Table 29 of the CS (hypoglycaemia events and volume depletion) or were otherwise considered important by the EAG (treatment discontinuation for any reason and any AE with outcome of death). Not all AEs used in the economic model for TA902 and/or listed as an AESI in Table 29 of the CS could be compared given data was not publicly available for the DELIVER trial; however, the EAG does not have any specific concerns that any not covered would differ between the two treatments (acute renal failure, hepatic injury, genital infection, symptomatic hypotension and bone fracture in Table 29 of the CS).

The EAG agrees with the company that AE profiles are likely to be similar for the two drugs; mean differences for the two trials are similar for both trials (mostly differences of <1.0%) and where larger differences are observed (i.e. for any SAE and cardiac failure event), the values indicate slightly larger reductions vs placebo for empagliflozin compared to dapagliflozin. Based on their experience in clinical practice, the EAG's clinical experts also had no concerns that the safety profiles of empagliflozin and dapagliflozin are different.

4.3.4 Additional evidence cited by the company

In addition to performing ITCs and comparing KCCQ and AE outcomes, the company cites evidence from a recent meta-analysis of EMPEROR-Preserved and DELIVER.[29] The EAG agrees that this meta-analysis suggests the two trials are similar with regards to outcomes analysed (primary composite outcome, HHF, CV mortality and AC mortality) and that no statistical heterogeneity was identified; this meta-analysis used outcome definitions that were more aligned in terms of definitions using secondary publications of EMPEROR-Preserved and DELIVER (some of which are in the appendix of the publication) and may not match some values used in the company's ITCs. This is because DELIVER individual patient data was available to the authors and could be used to align definitions to those used in EMPEROR-Preserved. The EAG's preferred analyses in Section 4.4.1 use some data from this paper but for the composite outcome, the EAG considered the alignments made were clearer in another paper.[28] The appendix of this meta-analysis also contains a comparison of proportions with KCCQ improvements or deteriorations in the two trials (also similar between the two trials with no statistical heterogeneity), data which has been included in ITCs by the EAG in Section 4.4.2.[29]

4.4 Additional work on clinical effectiveness undertaken by the EAG

In addition to validating the analyses performed by the company, the EAG performed some additional analyses. This was either new ITCs that were not performed by the company (KCCQ outcomes), repeating existing ITCs with outcome data that is more aligned between the trials and obtained from secondary publications of the EMPEROR-Preserved and DELIVER (primary composite outcome and CV mortality) or assessing the impact of removing the prior LVEF ≤40% subgroup from DELIVER on more outcomes, as the EAG identified this data for outcomes other than the primary composite outcome.

4.4.1 Aligning definitions for composite outcome, HHF and CV mortality outcomes

The EAG presents ITCs using alternative data to those presented in Table 3 above for the composite outcome and CV mortality, and comments on the anticipated impact on the HHF outcome given alternative data was not available for this outcome. For comparison, the results of the company's analyses are presented alongside in Table 4 below.

For the primary composite outcome (CV mortality or HHF), data from empagliflozin has been obtained from Anker *et al.* 2022;[28] while the values differ slightly to those in the meta-analysis mentioned in Section 4.3.4 (Vaduganathan *et al.* 2022; page 5 of the appendix),[29] it is clear that the data in Anker *et al.* 2022 accounts for the difference in hospitalisation length for HHF and includes UHFV events, as well as not including undetermined causes of death as CV mortality, while for Vaduganathan *et al.* 2022 the EAG is unsure if all of these alignments have been made. Data for DELIVER are the same as that used by the company in the CS, obtained from the primary DELIVER publication.[7] The EAG notes that this analysis has a small impact on results, with the HR point estimate favouring empagliflozin slightly more than in the company's analysis.

For CV mortality, Anker *et al.* 2022 also provided results for EMPEROR-Preserved when undetermined causes of death are not classed as CV deaths (as was the case in DELIVER).[28] These data were used in the EAG's analysis, with data for DELIVER obtained from its primary publication.[7] This also matches the data analysed for both trials in Vaduganathan *et al.* 2022.[29] Again, this analysis has a small impact on results, with the point estimate of the HR moving from a slight benefit of dapagliflozin, compared to empagliflozin, to a value of 1.00.

While definitions for the HHF outcome differed between the two trials (12 h vs 24 h hospitalisation; Table 2), better aligned data was not available for this outcome in any of the papers already cited.

However, the EAG considers the impact of this difference is likely to be very small; the Anker *et al.* 2022 paper (second and third rows of Table 1) shows that when the only change made to the original analysis of CV mortality or HHF in EMPEROR-Preserved is hospitalisation duration (using the Hicks criteria as in DELIVER) the HR and 95% CIs are unchanged, suggesting this single change had no impact.

The EAG considers that these additional analyses do not change its conclusions in Section 4.3.3.1 that empagliflozin and dapagliflozin are likely to be similar in terms of these outcomes and that these analyses may strengthen that view slightly, albeit with some uncertainty remaining based on 95% CIs. The EAG does, however, note the limitations associated with amending definitions *post-hoc* and that emergency room and UHFV visits for HF were not adjudicated in EMPEROR-Preserved.[28]

Table 4. Bucher analyses using aligned definitions and company's analyses for comparison

Comparison/outcome	EAG analysis		Company analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
CV mortality or HHF[a]				
EMPEROR-Preserved (empagliflozin vs background therapy)	0.76 (0.67 to 0.87)	<0.0001	0.79 (0.69 to 0.90)	<0.001
DELIVER (dapagliflozin vs background therapy)	0.82 (0.73 to 0.92)	0.001	0.82 (0.73 to 0.92)	<0.001
Empagliflozin vs dapagliflozin	*0.93 (0.78 to 1.10)*	*0.400*	*0.96 (0.81 to 1.15)*	*0.691*
CV mortality[b]				
EMPEROR-Preserved (empagliflozin vs background therapy)	0.88 (0.73 to 1.07)	0.214	0.91 (0.76 to 1.09)	0.310
DELIVER (dapagliflozin vs background therapy)	0.88 (0.74 to 1.05)	0.1678	0.88 (0.74 to 1.05)	0.1678
Empagliflozin vs dapagliflozin	*1.00 (0.77 to 1.30)*	*1.00*	*1.03 (0.80 to 1.33)*	*0.806*

[a]In the company's analysis, the trials differed with regards to duration of HHF required, inclusion of UHFV events and inclusion of undetermined deaths as CV deaths. In the EAG's analysis, data from Anker *et al.* 2022 was used, which provided EMPEROR-Preserved results when aligned to DELIVER definitions in terms of worsening HF (included UHFV in addition to HHF rather than just HHF, used the same time-point to define HHF and excluded deaths of undetermined cause from CV mortality).[28] Data for dapagliflozin was as used in the company's analysis; [b]in the company's analysis, the trials differed with regards to whether deaths of undetermined cause were included as CV deaths. In the EAG's analysis, data from Anker *et al.* 2022 was used, which provided EMPEROR-Preserved results when aligned to the definition used in DELIVER, which excluded deaths of undetermined cause from CV mortality.[28]

See Table 2 for more detail on the differences in definitions between the two trials.

Abbreviations: CI, confidence interval; CV, cardiovascular; EAG, External Assessment Group; HF, heart failure; HHF, hospitalisation for heart failure; HR, hazard ratio; UHFV, urgent heart failure visit.

4.4.2 *Indirect treatment comparisons for KCCQ outcomes*

The EAG performed formal ITCs for KCCQ outcomes, including change from baseline scores as a continuous outcome and dichotomous outcomes based on the proportions achieving ≥5-point improvements or deteriorations compared to baseline. Data for KCCQ-CSS and KCCQ-TSS are included given EMPEROR-Preserved focused on KCCQ-CSS and DELIVER focused on KCCQ-TSS. The EAG performed the ITCs of continuous data using R software version 4.2.0 with the "miniMeta" package version 0.2, and obtained p-values using Review Manager software version 5.3.[31-33] The analyses of dichotomous outcomes were performed using the same Microsoft® Excel sheets used by the company to perform ITCs for HRs of other outcomes in Section 4.3.3.1. Results are summarised below in Table 5 and Table 6.

Change from baseline data for EMPEROR-Preserved were obtained from the CTR for EMPEROR-Preserved;[6] although some data were reported in the CS (Table 22 of the CS), the EAG used alternative data identified in the CTR as this was more in line with the time-point and data included in the analysis for DELIVER (8 months and including on- and off-treatment values; see Table 2 and Section 4.3.3.2). However, for KCCQ-TSS, the EAG notes that the data analysed for EMPEROR-Preserved still includes imputation of 0.0 score for those that died (whereas DELIVER only includes surviving patient data) as equivalent data could not be found in the CTR. Change from baseline data were obtained from Kosiborod *et al.* 2023 for DELIVER.[27] The EAG notes that point estimates of differences favour dapagliflozin slightly but, as discussed in Section 4.3.3.2, differences are small and may not be clinically important, and there may be some bias favouring dapagliflozin in these analyses.

Dichotomous data was obtained from Butler *et al.* 2022 for EMPEROR-Preserved (as it could not be identified by the EAG in the CTR) and from Kosiborod *et al.* 2023 for DELIVER.[27, 30] Data presented is for 8 months in both trials and those who died before assessment at this time-point were counted as not improved or deteriorated in improvement and deterioration analyses, respectively. The EAG is unsure if the responder analyses from DELIVER also excluded patients with 8-month assessment after the date of the COVID-19 pandemic. Multiple imputation was used for those with missing values that had not died in both trials. For DELIVER, these details were confirmed based on the

description in the protocol included as supplementary material for the Solomon *et al.* 2022 publication as limited details were provided elsewhere.[7]

Dichotomous outcome results indicate that, based on the point estimates of odds ratios (ORs), the analyses for CSS improvement/deterioration and TSS deterioration favour dapagliflozin slightly, while for TSS improvement a slightly better result was seen for empagliflozin. However, most differences are small and none of these results are statistically significant. The EAG considers that, taking into account the fact that DELIVER results may also have excluded patients with 8-month assessments that occurred after the COVID-19 pandemic was declared and the bias this may introduce is against empagliflozin, the results for outcomes in Table 6 indicate that results are likely to be similar for empagliflozin and dapagliflozin, consistent with conclusions made in Section 4.3.3.2, although the EAG acknowledges this conclusion is not without uncertainty due to the 95% CIs observed.

Table 5. Bucher analyses of KCCQ outcomes performed by the EAG – change from baseline at 8 months

Comparison/outcome	EAG analysis	
	Mean difference (95% CI)	p-value
Change from baseline in KCCQ-CSS		
EMPEROR-Preserved (empagliflozin vs background therapy)[a]	[redacted]	[redacted]
DELIVER (dapagliflozin vs background therapy)[b]	2.30 (1.50 to 3.20)	<0.001
Empagliflozin vs dapagliflozin	[redacted]	[redacted]
Change from baseline in KCCQ-TSS[c]		
EMPEROR-Preserved (empagliflozin vs background therapy)[d]	[redacted]	[redacted]
DELIVER (dapagliflozin vs background therapy)[e]	2.40 (1.50 to 3.30)	NR
Empagliflozin vs dapagliflozin	[redacted]	[redacted]

[a]From Table 15.2.3.6:5 of the CTR;[6] [b]from central illustration of Kosiborod *et al.* 2023;[27] [c]definitions could not be aligned completely between trials and still differ with regards to including patients that died (included and score of 0.0 imputed for EMPEROR-Preserved and not included at all for DELIVER); [d]from Table 15.2.4.26.5:1 of the CTR;[6] [e]from Solomon *et al.* 2022.[7]

See Table 2 for more detail on the differences in definitions between the two trials.

Abbreviations: CI, confidence interval; CTR, clinical trial report; EAG, External Assessment Group; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; NR, not reported.

Table 6. Bucher analyses of KCCQ outcomes performed by the EAG – proportion with ≥5-point improvement or deterioration at 8 months

Comparison/outcome	EAG analysis	
	OR (95% CI)	p-value
≥5-point improvement in KCCQ-CSS		
EMPEROR-Preserved (empagliflozin vs background therapy)[a]	1.13 (1.01 to 1.26)	NR
DELIVER (dapagliflozin vs background therapy)[b]	1.17 (1.04 to 1.31)	NR
Empagliflozin vs dapagliflozin	*0.97 (0.82 to 1.13)*	*0.683*
≥5-point deterioration in KCCQ-CSS		
EMPEROR-Preserved (empagliflozin vs background therapy)[a]	0.83 (0.74 to 0.94)	NR
DELIVER (dapagliflozin vs background therapy)[b]	0.75 (0.65 to 0.86)	NR
Empagliflozin vs dapagliflozin	*1.11 (0.92 to 1.33)*	*0.284*
≥5-point improvement in KCCQ-TSS		
EMPEROR-Preserved (empagliflozin vs background therapy)[a]	1.17 (1.05 to 1.30)	NR
DELIVER (dapagliflozin vs background therapy)[b]	1.16 (1.03 to 1.30)	NR
Empagliflozin vs dapagliflozin	*1.01 (0.86 to 1.18)*	*0.922*
≥5-point deterioration in KCCQ-TSS		
EMPEROR-Preserved (empagliflozin vs background therapy)[a]	0.80 (0.71 to 0.90)	NR
DELIVER (dapagliflozin vs background therapy)[b]	0.76 (0.66 to 0.88)	NR
Empagliflozin vs dapagliflozin	*1.05 (0.87 to 1.27)*	*0.602*

[a]Data was obtained from Butler *et al.* 2022;[30] [b]data was obtained from Kosiborod *et al.* 2023.[27]

Abbreviations: CI, confidence interval; EAG, External Assessment Group; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; OR, odds ratio; NR, not reported.

4.4.3 *Removing the group with prior LVEF ≤40% from DELIVER*

The company explored the impact of using ITCs where the subgroup from DELIVER with prior LVEF ≤40% is excluded, as this data is included in the primary DELIVER publication.[7] The company only performed this analysis for the composite outcome but the EAG identified equivalent data for other

outcomes in a secondary paper.[26] The EAG has therefore performed ITCs using this subgroup from DELIVER for additional outcomes, which are included in Table 7 below.

Given the EAG's preferred analyses in Section 4.4.1 include outcome definitions for EMPEROR-Preserved that are aligned to DELIVER, the EAG uses this data for EMPEROR-Preserved in these analyses. This means the analysis for the composite outcome with the DELIVER subgroup data performed by the company (Table 26 of the CS) differs slightly to that presented here. The EAG notes that results are, however, similar but slightly more favourable for empagliflozin in the EAG's analysis (HR of 0.90 in EAG's analysis below and 0.94 in Table 26 of the CS for empagliflozin vs dapagliflozin). The EAG notes that the data used for the HHF and AC mortality outcomes for EMPEROR-Preserved is the same as in the company's original analyses as better aligned data could not be identified for HHF and AC mortality did not require alignment.

The results below indicate that removing the group with prior LVEF ≤40% from DELIVER leads to results that are slightly more favourable for empagliflozin than the original analyses, apart from HHF which remains the same. The most noticeable difference is for CV mortality, with a HR point estimate that now favours empagliflozin rather than a value of 1.00. In addition, the EAG notes that the slightly increased AC mortality in empagliflozin compared to dapagliflozin is alleviated slightly (HR point estimate 1.06 vs 1.04). One of the EAG's clinical experts anticipated that the inclusion of the group with prior LVEF ≤40% in DELIVER might lead to slightly more favourable outcomes in this trial compared to EMPEROR-Preserved. While the results below provide some support for this, the EAG notes limitations associated with using this subgroup data from DELIVER; based on baseline characteristics for those with prior LVEF ≤40% receiving dapagliflozin and placebo in this paper (the same breakdown by treatment received is not provided for the group with no prior measurement ≤40%),[26] baseline characteristics are likely to be more imbalanced between dapagliflozin and placebo arms compared to the overall DELIVER population (which may introduce bias in terms of relative treatment effects vs placebo obtained from this trial). In addition, there are more differences compared to EMPEROR-Preserved when this subgroup is focused on. Therefore, the EAG considers these analyses to be exploratory and considers it more appropriate that analyses where randomisation within both trials is maintained (Section 4.4.1) are focused on rather those using the DELIVER subgroup, as it may increase the differences between the two trials and introduce more bias.

While the EAG notes that a MAIC might be an option to align trials with regards to prior LVEF ≤40% inclusion and adjust for any additional differences vs EMPEROR-Preserved this introduces, this would not resolve the issue that dapagliflozin and placebo arms within this DELIVER subgroup may be imbalanced. In addition, MAICs interfere with or break randomisation and should only be used if there are differences in treatment effect modifiers between trials included in ITCs that are expected to confound results; it is unclear whether a MAIC In this scenario would result in more or less bias than Bucher analyses using the DELIVER subgroup data. The EAG, therefore, considers that this would not be a useful exercise. The EAG considers the results below to support the conclusions in Sections 4.3.3.1 and 4.4.1 that empagliflozin and dapagliflozin are likely to be similar in terms of these outcomes in the HFpEF/HFmrEF population.

Table 7. Bucher analyses where the subgroup with prior LVEF ≤40% in DELIVER are excluded

Comparison/outcome	Analysis with prior LVEF ≤40% removed from DELIVER[a]		Original EAG or company analysis including whole DELIVER population[b]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
CV mortality or HHF				
EMPEROR-Preserved (empagliflozin vs background therapy)	0.76 (0.67 to 0.87)	<0.0001	0.76 (0.67 to 0.87)	<0.0001
DELIVER (dapagliflozin vs background therapy)	0.84 (0.73 to 0.95)	NR	0.82 (0.73 to 0.92)	<0.001
Empagliflozin vs dapagliflozin	*0.90 (0.75 to 1.09)*	*0.294*	*0.93 (0.78 to 1.10)*	*0.400*
HHF				
EMPEROR-Preserved (empagliflozin vs background therapy)	0.71 (0.60 to 0.83)	<0.001	0.71 (0.60 to 0.83)	<0.001
DELIVER (dapagliflozin vs background therapy)	0.77 (0.66 to 0.90)	NR	0.77 (0.67 to 0.89)	<0.001
Empagliflozin vs dapagliflozin	*0.92 (0.74 to 1.15)*	*0.488*	*0.92 (0.74 to 1.14)*	*0.470*
CV mortality				
EMPEROR-Preserved (empagliflozin vs background therapy)	0.88 (0.73 to 1.07)	0.214	0.88 (0.73 to 1.07)	0.214
DELIVER (dapagliflozin vs background therapy)	0.95 (0.78 to 1.15)	NR	0.88 (0.74 to 1.05)	0.1678
Empagliflozin vs dapagliflozin	*0.93 (0.71 to 1.22)*	*0.594*	*1.00 (0.77 to 1.30)*	*1.00*

AC mortality				
EMPEROR-Preserved (empagliflozin vs background therapy)	1.00 (0.87 to 1.15)	1.000	1.00 (0.87 to 1.15)	1.000
DELIVER (dapagliflozin vs background therapy)	0.96 (0.83 to 1.10)	NR	0.94 (0.83 to 1.07)	0.3425
Empagliflozin vs dapagliflozin	*1.04 (0.85 to 1.27)*	*0.700*	*1.06 (0.88 to 1.28)*	*0.531*

[a]Results for the DELIVER subgroup were obtained from Vardeny *et al.* 2022;[26] [b]results in this column for the composite outcome (CV mortality of HHF) and CV mortality are from Section 4.4.1 as the EAG performed analyses where outcome definitions were better aligned. For HHF and AC mortality, results are from Section 4.3.3.1 as no additional analysis to align definitions could be performed/was required. See Table 2 for more detail on the differences in definitions between the two trials.

Abbreviations: AC, all-cause; CI, confidence interval; CV, cardiovascular; EAG, External Assessment Group; HHF, hospitalisation for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NR, not reported.

4.5 Conclusions of the clinical effectiveness section

Evidence for the efficacy and safety of empagliflozin in the population specified in the decision problem (HFpEF/HFmrEF) and NICE final scope is available from EMPEROR-Preserved.[6, 8] There are no major concerns about risk of bias in this trial and while some differences compared to UK clinical practice were noted in the STA that was originally performed,[9] none of these were considered to be major issues and it is considered to be a reasonable reflection of this population in UK clinical practice (Sections 3.1 and 4.2.1).

EMPEROR-Preserved uses the dose of empagliflozin outlined in its marketing authorisation for CHF and compares outcomes to placebo (Sections 3.2 and 4.2.1).[2, 6] Point estimates for most efficacy outcomes, including HHF, CV mortality and KCCQ scores, indicate benefits of empagliflozin compared to placebo, although not all are statistically significant. In addition, point estimates suggested no difference in AC mortality between empagliflozin and placebo. There are no concerns that empagliflozin increases the risk of certain AEs compared to placebo (Section 4.2.2).

The EAG highlights that there appears to be an increased risk of non-CV death with empagliflozin compared to placebo and is unable to explain this observation. The EAG does not consider it to be a major issue that would prevent a CCA being considered appropriate but considers it worthy of note (Section 4.2.2.1).

Comparisons against dapagliflozin were performed by the company via Bucher analyses or visual comparisons of data. These covered all outcomes relevant to the economic model of TA902, where dapagliflozin is recommended by NICE for HFpEF/HFmrEF (Section 4.3).[1] Differences discussed between patient characteristics and trial design are unlikely to have a large impact on the efficacy or empagliflozin or dapagliflozin and Bucher analyses are considered reasonable (Sections 4.3.1, 4.3.2 and 9.3). Differences in outcome definitions between the trials were explored by the company and/or EAG in additional analyses where possible (Sections 4.3.2 and 4.4).

Based on the company's ITCs, the EAG concludes that empagliflozin and dapagliflozin are likely to be similar in terms of composite, HHF and mortality outcomes; point estimates suggest a benefit of empagliflozin for the composite outcome and HHF, but a slight benefit of dapagliflozin for CV mortality and AC mortality (no statistically significant differences; Section 4.3.3.1). The EAG's analyses provide results when better aligned definitions are used for the composite outcome and CV mortality and further support the idea that the two drugs are similar; of particular note is the fact that the point estimate of the HR for CV mortality moves from a slight benefit of dapagliflozin (1.03) to a value of 1.00 suggesting equivalence (Section 4.4.1).

A key difference between EMPEROR-Preserved and DELIVER was the inclusion of those with prior LVEF ≤40% in DELIVER but not in EMPEROR-Preserved. The impact of this on efficacy outcomes discussed above was explored by the company and the EAG (Sections 4.3.2 and 4.4.3); point estimates for all outcomes either increase the benefit of empagliflozin vs dapagliflozin or favour dapagliflozin less than in the original analyses; of note, the slight benefit of dapagliflozin in terms of AC mortality is reduced (HR point estimate 1.06 vs 1.04) and the HR point estimate of 1.00 for CV mortality moves to one that suggests a slight benefit of empagliflozin (HR point estimate 1.00 vs 0.92). However, the EAG notes that none of these differences are statistically significant either and limitations of these analyses mean they are considered to be exploratory (Section 4.4.3).

Based on the formal ITCs of KCCQ outcomes performed by the EAG, the two drugs are also likely to have a similar impact on KCCQ outcomes. While the EAG used definitions and time-points that were as aligned as possible between the two trials for KCCQ outcomes, some bias favouring dapagliflozin may remain given that patients in DELIVER that had their 8-month follow-up after the date the COVID-19 pandemic was declared were not included at that time-point (Sections 4.3.3.2 and 4.4.2). There are no concerns that the safety profile differs between the two drugs (Section 4.3.3.3).

While the EAG notes that uncertainty in conclusions for efficacy outcomes based on the ITCs remains based on 95% CIs, taken together with clinical expert feedback to the EAG that there is no appreciable difference between the two drugs when used currently to treat HFrEF, the fact that they have the same mechanism of action and that they are used at the same dose and administration schedule, the EAG considers outcomes are likely to be similar between empagliflozin and dapagliflozin in patients with HFpEF/HFmrEF.

5 Summary of the EAG's critique of cost comparison evidence submitted

The company developed a cost-comparison (CC) model which assessed empagliflozin against dapagliflozin in patients with chronic heart failure (CHF) with preserved or mildly reduced left ventricular ejection fraction (LVEF; HFpEF or HFmrEF). Based on the discussion in Section 4.3, the External Assessment Group (EAG) agrees with the company that the two treatments have similar clinical efficacy and comparable safety profiles.

The company's deterministic base case results are given in Table 8. The company considered that the total annual cost for the two drugs is the same (i.e., £726.78), which accounted for treatment acquisition costs, and six annual general practitioner (GP) visits. The company also conducted an analysis where a hospitalisation for heart failure event (HHF) per year is assumed, with the total annual cost remaining equivalent for both treatments. Finally, the company also considered the impact of including the cost of cardiovascular (CV) mortality in the model, which did not alter the conclusions of similar costs generated between the two treatments.

Table 8. Company's base case results

Interventions	Empagliflozin	Dapagliflozin
Treatment acquisition cost per year	£477.30	£477.30
GP visits, cost per year	£249.48	£249.48
Total cost per year	£726.78	£726.78
Incremental cost per year	£0	
HHF cost per event	£2,542	£2,542
Total cost per year, including 1 HHF event*	£3,268.78	£3,268.78
Incremental cost per year, including 1 HHF event*	£0	
CV mortality cost	£1,452	£1,452
Total cost per year, including CV mortality**	£4720.78	£4720.78
Incremental cost per year, including CV mortality**	£0	

* Assuming treatment acquisition cost, 6 GP visits per year, and one HHF event

** Assuming treatment acquisition cost, 6 GP visits per year, one HHF event, and CV death

Abbreviations: CV, cardiovascular, GP, general practitioner; HHF, hospitalisation for heart failure.

5.1 Resource use and costs

The EAG agrees that the annual treatment acquisition costs for empagliflozin and dapagliflozin are the same. The EAG notes some uncertainty in the company's assumption of six annual GP visits assumed in the model as the previous single technology appraisal (STA) submission to the National Institute for Health and Care Excellence (NICE) in 2022 (Draft Guidance published in February 2023)[9] for empagliflozin patients with HFpEF or HFmrEF assumed a higher number of annual GP visits. Nonetheless, the EAG has no reason to believe that HFpEF or HFmrEF patients would require a different number of GP visits depending on being treated with empagliflozin or dapagliflozin, therefore, rendering the frequency (and the cost) of GP visits irrelevant in the context of a CC. The same is true for the inclusion of costs for HHF and CV deaths in the model, given the EAG's assessment that these events are likely to be similar under both treatments (see Sections 4.3, 4.4 and 4.5).

5.2 Summary statement

The EAG considers that a CC is appropriate and agrees with the company that empagliflozin and dapagliflozin generate similar costs to the NHS.

6 Equalities and innovation

The External Assessment Group (EAG) is unaware of any equality or innovation considerations, other than those described by the company in Section 3.5 regarding primary and secondary care prescription; however, this was already discussed by the committee as part of the single technology appraisal (STA) that was performed for empagliflozin in this indication and it was concluded that empagliflozin, if recommended in those with chronic heart failure and preserved or mildly reduced left ventricular ejection fraction (≥40%; HFpEF/HFmrEF), *"would be started on the advice of a heart failure specialist who can determine the most appropriate treatment"*.[19]

7 EAG commentary of the robustness of the evidence submitted by the company

The External Assessment Group (EAG) does not consider any of the issues below would prevent a cost-comparison appraisal (CCA) being appropriate but notes them as limitations or factors to be aware of.

Clinical

Conclusions are made based on indirect treatment comparisons and there is no direct evidence comparing empagliflozin and dapagliflozin. While the EAG considers the analyses presented in this report are a robust alternative and has no major concerns about differences between trials, it notes that direct evidence would increase the certainty with which conclusions about similarity could be made.

Data analysed in the company's analyses were not completely aligned in terms of definitions and time-points for many outcomes, to the detriment of empagliflozin in most cases, but the EAG's additional analyses use data that are better aligned.

The EAG highlights that point estimates of hazard ratios obtained from EMPEROR-Preserved for empagliflozin vs placebo in terms of cardiovascular (CV) and all-cause mortality outcomes suggest that there may be a benefit for empagliflozin on CV mortality but increased deaths vs placebo due to non-CV causes. It notes that this may also be observed in DELIVER for dapagliflozin vs placebo (to a lesser extent) and the reason for this observation is unclear. It does not consider this to be a major issue in terms of the appropriateness of a CCA but considers it worthy of note.

Economic

While the EAG has some reservations around the resource use used in the company's model, as dapagliflozin and empagliflozin have the same acquisition cost and are expected to be used in the same way in the NHS, resource use would have no impact on these treatments being considered to incur the same costs.

8 References

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9 Appendices

9.1 EAG's quality assessment of EMPEROR-Preserved and DELIVER

Table 9. A summary of the EAG's critique of the design, conduct and analysis of the DELIVER trial

Aspect of trial design or conduct	EMPEROR-Preserved	DELIVER
Randomisation	**Appropriate** Randomised 1:1 via IRT using a permuted block design with a computer pseudo-random number generator. Randomisation was stratified by geographical location, history of diabetes (diabetes, pre-diabetes or no diabetes), eGFR at screening (<60 vs ≥60 ml/min/1.73 m^2) and LVEF (<50% vs ≥50%).	**Appropriate** Randomised 1:1 using an IWRS in balanced blocks. Randomisation was stratified by T2DM status at baseline.
Concealment of treatment allocation	**Appropriate** IRT was used for randomisation. Access to the randomisation code was said to be [redacted] to ensure relevant parties were blinded to treatment group assignment. [redacted]	**Appropriate** While it is unclear whether the randomisation schedule was kept by a third party, this is likely as a third party was described as being responsible for the set-up and maintenance of the IWRS for randomisation and drug dispensation.
Eligibility criteria	**Appropriate** The EAG's clinical experts at the time of the STA for empagliflozin in this indication had no major concerns about inclusion and exclusion criteria for this trial.[9] The EAG considers the trial population to reflect that in the NICE final scope well (see Section 3.1).[8] Differences in inclusion criteria between EMPEROR-Preserved and DELIVER are discussed in Sections 4.3, 4.4 and Appendix 9.3.	**Appropriate** The EAG has no major concerns about inclusion and exclusion criteria for DELIVER and considers that those included are a good match to the NICE final scope set out for this CCA.[8] The EAG notes that the most notable difference is the inclusion of patients with prior LVEF ≤40% in DELIVER (and not in EMPEROR-Preserved) but does not consider that this makes it less applicable to the population of interest (see Sections 4.3, 4.4 and Appendix 9.3 for further discussion of differences between studies).
Blinding	**Appropriate** The study was double-blind, with participants, investigators and independent clinical event committee's blinded to treatment assignment. Anyone involved in trial conduct or analysis, or with any other interest in the trial,	**Appropriate** The trial was described as being double-blind. Patients, investigators and the adjudication committee were blind to treatment assignment. Dapagliflozin and placebo treatments are also described as matching.

	remained blinded to assigned treatments until after the database lock. Procedures for emergency unblinding were in place but were not required. Empagliflozin and placebo treatments are also described as matching.	
Baseline characteristics	**Well-balanced between groups** Baseline characteristics were similar between empagliflozin and placebo groups for the ITT population (see Section B.3.3 of the CS and Table 11 of this report). Applicability of the baseline characteristics (including use of standard of care treatments) in the trial to the decision problem and UK practice is discussed in Section 3 and Appendix 9.3. They are considered to be a reasonable reflection of a population in UK practice.	**Well-balanced between groups** Baseline characteristics for the FAS population are well-balanced between dapagliflozin and placebo groups, including demographics, HF history, comorbidities and standard of care treatments (see Appendix 9.3). As discussed in Section 4.3.2 and Appendix 9.3, the EAG's clinical experts for this CCA did not consider there to be any important differences compared to EMPEROR-Preserved.
Dropouts	**Balanced between groups** As indicated in Figure 7 of the CS, 23.2% and 23.4% of empagliflozin and placebo groups, respectively, either did not start or discontinued treatment. In terms of the primary composite outcome, incomplete follow-up was reported for similar proportions in each arm (2.8% vs 2.9%).	**Balanced between groups** As indicated in published supplementary material for DELIVER, 14.3% in dapagliflozin and placebo groups either did not start or discontinued treatment. In terms of the primary composite outcome, incomplete follow-up was reported for similar proportions in each arm, although slightly lower for the placebo arm (9.3% vs 7.3%).[7]
Statistical analysis		
Sample size and power	**No concerns** The study was event driven. In the ITT population, there was a target of 841 primary outcomes to achieve a power of 90% for a two-sided test with α=0.05 and to detect a HR of 0.80. A total of 4126 patients needed to be randomised to empagliflozin or placebo in a 1:1 manner. The trial randomised ~6000 patients and 926 primary outcomes occurred by the end of the trial and . The EAG notes that the trial was not powered to assess individual components of the primary outcome or other outcomes reported in the trial.	**No concerns** The study was event driven. In the FAS population, 1117 events for the composite outcome were estimated to provide 90% power, assuming a HR of 0.80 between dapagliflozin and placebo. A required sample size of 6100 patients was calculated. A total of n=1122 events were observed in the primary end-point analysis and ~6300 were randomised. The EAG notes that this was an amendment to the protocol based on the ongoing blinded monitoring of event accrual, as the original plan involved fewer patients and primary outcome events.[7] The EAG notes that the trial was not powered to assess individual components of the primary outcome or other outcomes reported in the trial.

Analysis for estimate of effect	**Appropriate** For outcomes covered as part of this CCA, most were analysed in the ITT population (randomised set). This includes the primary composite outcome and other time-to-event outcomes. AEs were analysed in those that received at least one treatment with empagliflozin or placebo. As noted in Section 4.3.2 and Appendix 9.3, the primary analysis for KCCQ-CSS was in the treated set (as for AEs) but only including on-treatment values. While the EAG considers this may introduce bias, data for an alternative analysis using the ITT set and on- and off-treatment values was available in the CTR.	**Appropriate but some concerns for KCCQ** For outcomes covered as part of this CCA, most were analysed in the FAS (randomised set). This includes the primary composite outcome and other time-to-event outcomes. AEs were in those that received at least one treatment with dapagliflozin or placebo. As noted in Section 4.3.2 and Appendix 9.3, published data for the primary KCCQ-TSS outcome in DELIVER is based solely on the group that had their 8-month assessment performed prior to 11 March 2020, when COVID-19 was declared a pandemic. The impact of this analysis focused on data before COVID-19 is unclear and the EAG notes this is a difference between EMPEROR-Preserved and DELIVER.
Handling of missing data	**Appropriate but some concerns for KCCQ analyses** No data was imputed for safety or time-to-event endpoints. See Table 2 of Section 4.3.2 in this report for more detail about missing data handling in KCCQ analyses; the EAG considers that the MAR assumption may not be appropriate for missing KCCQ data in survivors.	**Appropriate but some concerns for KCCQ analyses** For event-based outcomes, such as the primary composite outcome, missing data is described as being low. Patients were censored at the last clinical event assessment and follow-up was good with few having unknown vital status. See Table 2 of Section 4.3.2 in this report for more detail about missing data handling in KCCQ analyses; the EAG considers that the MAR assumption may not be appropriate for missing KCCQ data in survivors.
Outcome assessment	**Appropriate** Independent external clinical event committees evaluated all reported and potential clinical events in a blinded manner. Criteria required to meet outcome definitions were clear. The EAG considers the outcomes assessed to be appropriate and cover those outlined in the NICE final scope.[8] All prespecified outcomes are reported either in the CS or the CTR. The EAG notes some differences with regards to outcome definitions compared to DELIVER (see Section 4.3.2) but that aligned definitions could be obtained for some outcomes (Section 4.4).	**Appropriate** Independent clinical event committees adjudicated clinical events in a blinded manner. Criteria required to meet outcome definitions were clear. The EAG considers the outcomes assessed to be appropriate and that they are similar to those included for EMPEROR-Preserved. The EAG considers that all prespecified outcomes have been reported.

Abbreviations: AEs, adverse events; CCA, cost-comparison appraisal; CS, company submission; CTR, clinical trial report; EAG, External Assessment Group; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; IRT, interactive response technology; ITT, intention to treat; IWRS, interactive web response system; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – Total Symptom Score; LVEF, left ventricular ejection fraction; MAR, missing at random; NICE, National Institute for Health and Care Excellence; STA, single technology appraisal; T2DM, type 2 diabetes mellitus; UK, United Kingdom.

9.2 EAG's critique of the SLR

Table 10. A summary of the EAG's critique of the SLR

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**The EAG considers the sources and dates searched to be comprehensive.** Databases searched: • Embase; MEDLINE; MEDLINE In-Process; the Cochrane Library (including CENTRAL and CDSR) The first two searches (May 2020 and October 2020) included RCT filters for all databases except MEDLINE In-Process, and MEDLINE and Embase were searched via Embase.com, with MEDLINE In-Process searched separately via Pubmed.com. Later searches (from July 2021 to January 2023) involved searching MEDLINE and Embase via Ovid with RCT filters used. Conference proceedings (2018 to 2023 – last accessed February 2023): • American Heart Association (AHA), European Society of Cardiology Congress (ESC), American College of Cardiology (ACC) Bibliographies of key systematic reviews and meta-analyses were screened to ensure that initial searches captured all the relevant studies.
Search strategies	Appendix D.1.1	**The EAG is satisfied that the company's searches have identified all evidence relevant to the decision problem.** The electronic database searches were performed from database inception to date of the SLR, without any time limit. The electronic databases were searched using a combination of MeSH/EMTREE terms, and free-text terms for both disease and intervention facets. All free-text terms were limited to abstracts, titles and keyword headings.
Inclusion criteria	Appendix D.1.1 (Table 18)	**The EAG considers that no studies of relevance to this CCA have been inappropriately excluded** The eligibility criteria matched the population outlined in the NICE final scope.[8] Criteria for the intervention and comparator were wider than that specified in the NICE scope and covered dapagliflozin which was the comparator in this CCA. The list of outcomes in Table 18 of Appendix D of the CS differed slightly to the NICE scope but this list is described as tentative rather than exhaustive. Records were limited to English language studies. A reference list of all records excluded at full text review was provided.

		The EAG reviewed studies excluded at this stage and is satisfied that EMPEROR-Preserved and DELIVER are the only relevant studies for this CCA retrieved for empagliflozin and dapagliflozin, respectively, in HFpEF/HFmrEF. The EAG agrees with the company's reasoning in Table 9 of the CS when explaining why only EMPEROR-Preserved was included for empagliflozin in this CCA; the population was not relevant (e.g. HFrEF or acute HF) in most of these and not reflective of HFpEF/HFrEF. While EMPERIAL-Preserved and EMPA-Vision are other studies including patients with HFpEF/HFmrEF,[20, 21] the EAG notes that the only relevant outcome from these trials would be KCCQ score, with other outcomes focused on functional measures such as exercise capacity. In addition, KCCQ data is at 12 weeks in these studies which is much shorter than that captured in EMPEROR-Preserved.
Screening	Appendix D.1.1	**The EAG considers the reporting of methods for screening to be adequate** From the original review to the fourth SLR update, title/abstract screening and full text screening was conducted by two independent reviewers. For the most recent update, literature review software (DistillerSR) was employed. Studies already included in the review were used to train the software. An independent reviewer reviewed all references and a second reviewer screened 95% of the references that were ranked by the software as eligible for inclusion. Remaining references were then auto-screened by DistillerSR. Any discrepancy was resolved by a third, independent reviewer. While the EAG has no experience of the software used for this final update and how likely it may be to exclude studies that are actually relevant, it considers the fact that at least one reviewer reviewed all references to limit this risk somewhat. However, the EAG notes that having only one reviewer screen all references may be considered less robust compared to two reviewers as in the original and earlier update searches. As noted above under "inclusion criteria", the EAG is not aware of other studies for empagliflozin or dapagliflozin not already included in this CCA and, therefore, does not consider this to be an issue in this instance.
Data extraction	Appendix D.1.1	**The EAG considers methods for data extraction to be appropriate** One reviewer extracted the data from the included full-text articles. All extracted data were quality checked against the original source article by the second reviewer.
Tool for quality assessment of included study or studies	Appendix D.1.3 (Tables 29 and 30)	**The EAG agrees with the company's choice of quality assessment tool of RCTs.** Study quality was assessed using recommendations given in the NICE manufacturer's submission template.

Abbreviations: CCA, cost-comparison appraisal; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Controlled Register of Trials; CS, company submission; EAG: External Assessment Group; HF, heart failure; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review.

9.3 Comparison of baseline characteristics, standard of care treatments and study design in EMPEROR-Preserved and DELIVER trials

With regards to baseline characteristics, the EAG agrees that for many characteristics, the two trials are similar. However, it notes that differences for race, region, New York Heart Association (NYHA) class II vs III, systolic blood pressure (SBP), proportion with LVEF ≥60%, diabetes mellitus (DM) and baseline atrial fibrillation or flutter are more noticeable (Table 11). Some of these differences suggest that the DELIVER trial may be a sicker population (higher proportions in DELIVER with NYHA class III, lower proportions with LVEF ≥60% and more patients with atrial fibrillation or flutter) but there were more patients in EMPEROR-Preserved with DM, which may mean prognosis is more complex (the EAG also notes that empagliflozin and dapagliflozin can also be used to treat type 2 DM [T2DM]; Section 2). The potential impact of differences in SBP, race and region on outcomes with either drug is unclear.

The EAG's clinical experts considered the differences between trials mentioned above to be small and did not anticipate they would impact relative treatment effects for either of the two drugs. Based on this feedback and the fact that characteristics are well-balanced between intervention and placebo arms in each trial, the EAG is satisfied that there are no large differences in baseline characteristics that necessitates other methods for ITCs, such as MAICs. Both of the EAG's clinical experts noted that the biggest difference between the two trials concerns the inclusion or exclusion of those with a prior LVEF ≤40%, with one noting that they would expect outcomes to be slightly better in the group that have had a prior measurement ≤40%; if true, this would mean that ITCs including full populations from both trials may favour dapagliflozin slightly. This has been explored by the company and the EAG in Sections 4.3.3.1 and 4.4.3.

Similarly, the EAG noted some slight differences in terms of background standard of care treatments used; overall, the clinical experts advising the EAG were not concerned that these were large enough differences to impact relative treatment outcomes. One clinical expert noted that the proportions using loop diuretics is low in both trials compared to what would be expected in UK clinical practice; as patients not using these are more likely *not* to have genuine heart failure and the efficacy of treatments might subsequently be reduced in these patients, and the proportion using them is lower in EMPEROR-Preserved, this may have reduced the efficacy of empagliflozin slightly compared to dapagliflozin in any ITCs. However, they considered that any impact on outcomes from ITCs comparing empagliflozin and dapagliflozin would be small. Given it is not possible to confirm why fewer patients compared to practice were using loop diuretics in the trials and it may be unrelated to CHF diagnosis, the EAG does not consider this to be a major issue, particularly as it is unlikely to have a large impact on results.

Table 11. Comparison of baseline patient characteristics between EMPEROR-Preserved and DELIVER – adapted from Table 23 of the CS[a]

Baseline characteristic	EMPEROR-Preserved		DELIVER	
	Empagliflozin (N=2997)	Placebo (N=2991)	Dapagliflozin (N=3131)	Placebo (N=3132)
Age, mean (SD)	71.8 (9.3)	71.9 (9.6)	71.8 (9.6)	71.5 (9.5)
Female sex, n (%)	1338 (44.6)	1338 (44.7)	1364 (43.6)	1383 (44.2)
BMI, mean (SD)	29.77 (5.8)	29.9 (5.9)	29.8 (6.2)	29.9 (6.1)
Race				
White, n (%)	2286 (76.3)	2256 (75.4)	2214 (70.7)	2225 (71)
Black, n (%)	133 (4.4)	125 (4.2)	81 (2.6)	78 (2.5)
Asian, n (%)	413 (13.8)	411 (13.7)	630 (20.1)	644 (20.6)
Other race, n (%)	165 (5.5)	199 (6.7)	206 (6.6)	185 (5.9)
Region				
North America, n (%)	360 (12.0)	359 (12.0)	428 (13.7)	423 (13.5)
South/Latin America, n (%)	758 (25.3)	757 (25.3)	602 (19.2)	579 (18.5)
Europe or Saudi Arabia, n (%)	1346 (44.9)*	1343 (44.9)*	1494 (47.7)	1511 (48.2)
Asia, n (%)	343 (11.4)	343 (11.5)	607 (19.4)	619 (19.8)
Other, n (%)	190 (6.3)	189 (6.3)	-	-
NYHA functional classification				
I, n (%)	3 (0.1)	1 (<0.1)	-	1 (<0.1)
II, n (%)	2432 (81.1)	2451 (81.9)	2314 (73.9)	2399 (76.6)
III, n (%)	552 (18.4)	531 (17.8)	807 (25.8)	724 (23.1)
IV, n (%)	10 (0.3)	8 (0.3)	10 (0.3)	8 (0.3)
Heart rate – beats/min, mean (SD)	70.4 (12)	70.3 (11.8)	72 (12.0)	71 (12.0)
Systolic blood pressure – mmHg, mean (SD)	131.8 (15.6)	131.9 (15.7)	128 (15.0)	128 (15.0)
LVEF				
LVEF – %, mean (SD)	54.3 (8.8)	54.3 (8.8)	54 (8.6)	54.3 (8.9)
LVEF >40% to <50% — no. (%)	995 (33.2)	988 (33)	1067 (34.1)	1049 (33.5)
LVEF ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)	1133 (36.2)	1123 (35.9)
LVEF ≥60% — no. (%)	974 (32.5)	973 (32.5)	931 (29.7)	960 (30.7)
Medical history				
HHF past 12 months, n (%)	669 (23.3)	670 (22.4)	-[b]	-[b]
Hypertension, n (%)	2721 (90.8)	2703 (90.4)	2755 (88)	2798 (89.3)
DM, n (%)	1466 (48.9)	1472 (49.2)	1401 (44.7)	1405 (44.9)
Previous LVEF ≤40%, n (%)	0	0	572 (18.3)	579 (18.5)
Atrial fibrillation/flutter at baseline ECG n (%)	1064 (35.6)	1016 (33.9)	1327 (42.4)	1317 (42.1)
eGFR – ml/min/1.73 m^2 n (%)	60.6 (19.8)	60.6 (19.9)	61 (19.0)	61 (19.0)

Standard of care treatments (N,[%])				
ACEI	1199 (40.0)	1210 (40.5)	1144 (36.5)	1151 (36.7)
ACEI/ARB	2367 (79.0)	2338 (78.2)	NR	NR
ARB	1177 (39.3)	1139 (38.1)	1133 (36.2)	1139 (36.4)
Sacubitril-valsartan	NR	NR	165 (5.3)	136 (4.3)
ACEI/ARB/ARNI	2428 (81.0)	2404 (80.4)	NR	NR
ARNI	65 (2.2)	69 (2.3)	301 (4.8%) overall	
Beta-blocker	2598 (86.7)	2569 (85.9)	2592 (82.8)	2585 (82.5)
Diuretics	2563 (85.5)	2600 (86.9)	NR	NR
Loop diuretic (loop or high-celling diuretics for EMPEROR-Preserved)	2030 (67.7)	2024 (67.7)	2403 (76.7)	2408 (76.9)
MRA	1119 (37.3)	1125 (37.6)	1340 (42.8)	1327 (42.4)

[a]Data taken from Table 23 of the CS, Table S4 of supplementary material 3 of the primary publication (or a secondary publication for proportion with ARNI) for DELIVER and the CTR for EMPEROR-Preserved;[6, 7, 34] [b]HHF rates within 12 months were not reported for DELIVER, but HHF rates at any point in the past were 40.6% vs 40.5% in dapagliflozin and placebo arms, respectively. *Europe only

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CS, company submission; CTR, clinical trial report; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.

Table 12. Comparison of study design between EMPEROR-Preserved and DELIVER – adapted from Table 15 of the CS[a]

Study feature	EMPEROR-Preserved	DELIVER
Trial number	NCT03057951	NCT03619213
Trial design	Phase III, randomised, double-blind, event-driven, placebo-controlled with parallel assignment.	Phase III, randomised, double-blind, event-driven, placebo-controlled trial with parallel assignment.
Eligibility criteria	• Males and females aged ≥18 years (≥20 years for Japan); • Chronic HF with LVEF >40% diagnosed for at least 3 months, currently in NYHA class II-IV (LVEF confirmed within past 6 months); • NT-proBNP >300 pg/ml if no AF/AFl or >900 pg/ml if AF/AFl; • Documented structural heart disease (LA enlargement or LV hypertrophy) within 6 months OR	• Males and females aged ≥40 years; • Symptomatic CHF with LVEF >40% diagnosed for at least 6 weeks with at least intermittent need for diuretic treatment, currently in NYHA class II-IV (LVEF confirmed within last 12 months); • NT-proBNP ≥300 pg/ml if no AF/AFl or ≥600 pg/ml if AF/AFl; • Evidence of structural heart disease (LA enlargement or LV

	HHF documented within 12 months prior to screening; • If prescribed, oral diuretics must be stable for at least one week prior to randomisation; • BMI <45 kg/m^2.	hypertrophy) within last 12 months • Patients could be ambulatory or hospitalised but must be off IV HF treatment (including diuretics) for at least 12 h prior to enrolment and 24 h prior to randomisation; • BMI ≤50 kg/m^2.
Exclusion criteria (note only those that were considered to differ slightly between trials are listed here)	• Prior LVEF ≤40% under stable conditions led to exclusion; • Type 1 diabetes included but very small proportion; • eGFR <20 ml/min/1.73 m^2 excluded; • SBP <100 mmHg or symptomatic hypotension; • SBP >150 mmHg if not treated with ≥3 BP lowering medications or ≥180 mmHg irrespective of treatments; • Life expectancy <1 year due to any disease other than heart failure based on opinion of investigator.	• Those with prior LVEF ≤40% could be included; • Type 1 diabetes excluded from this study; • eGFR <25 ml/min/1.73 m^2 excluded; • SBP <95 mmHg, no mention of symptomatic hypotension; • SBP ≥160 mmHg if not treated with ≥3 BP lowering medications or ≥180 mmHg irrespective of treatments; • Life expectancy <2 years due to any non-CV condition based on investigator judgement.
Settings and locations where data were collected	622 locations in 23 countries (Poland, Czech Republic, Hungary, Germany, the Netherlands, Italy, Romania, Spain, Belgium, UK, Brazil, Argentina, Colombia, Mexico, US, Canada, Japan, China, Korea, Singapore, South Africa, Australia and India). From the UK, 53 patients enrolled and 25 of these were randomised and treated.	353 locations in 20 countries (Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Hungary, Japan, Mexico, the Netherlands, Peru, Poland, Romania, Russia, Saudi Arabia, Spain, Taiwan, USA, Vietnam). No UK patients enrolled.
Intervention and comparators	Intervention: 10 mg oral empagliflozin once daily in addition to background treatment (i.e. treatments for CV comorbidities). Comparator: Placebo in addition to background treatment as above.	Intervention: 10 mg oral dapagliflozin once daily in addition to background treatment (i.e. treatments for CV comorbidities). Comparator: Placebo in addition to background treatment as above.
Permitted and disallowed concomitant medication	Any SGLT2 inhibitor or combined SGLT1 and 2 inhibitors were disallowed, other than the blinded trial medication.	Any SGLT2 inhibitor use other than the blinded trial medication was prohibited for the study duration.
Primary outcomes	Composite of CV death or HHF (analysed as time to first event).	Composite of worsening HF (HHF or UHFV) or CV death (analysed as time to first event).

Analysis sets[b]	ITT for primary end-point and time-to-event outcomes covered in this report. Analyses were performed in the TS for AEs. Primary analysis of KCCQ was performed in the TS and used on-treatment values only (OC-OT analysis); analysis in ITT set and including on and off-treatment values also available (OC-AD analysis).	ITT for primary end-point and other time-to-event outcomes covered in this report. Analyses were performed in the SAS for AEs (equivalent to TS in EMPEROR-Preserved). Primary analysis of KCCQ was performed using ITT set, including all data irrespective of whether patient has discontinued treatment. Excluded patients whose 8-month assessment was after COVID-19 outbreak (defined as 11th March 2020).
Trial duration (median)	26.2 months	27.6 months

[a]Data taken from Table 15 of the CS, publication and associated supplementary material for DELIVER and the CTR for EMPEROR-Preserved;[6, 7] [b]ITT represents all randomised patients, whether treated or not, analysed according to their randomised treatment and TS/SAS represent those randomised and receiving at least one dose of intervention or placebo treatment, analysed according to treatment randomised to.

Abbreviations: AEs, adverse events; AF, atrial fibrillation, AFl, atrial flutter; BMI, body mass index; BP, blood pressure; CHF, chronic heart failure; CS, company submission; CTR, clinical trial report; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; ITT, intention to treat; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OC-AD, observed case including data after treatment discontinuation as well as on-treatment data; OC-OT, observed case including on-treatment data only; SAS, safety analysis set; SBP, systolic blood pressure; SGLT, sodium-glucose co-transporter; TS, treated set; UHFV, urgent heart failure visit; UK, United Kingdom; USA, United States of America.

9.4 Comparison of adverse events between EMPEROR-Preserved and DELIVER trials

Table 13. Summary of AEs in EMPEROR-Preserved and DELIVER – adapted from Table 30 of the CS

AE category	EMPEROR-Preserved			DELIVER		
	Empagliflozin (N=2996) n (%)	Placebo (N=2989) n (%)	Mean difference (%)	Dapagliflozin (N=3126) n (%)	Placebo (N=3127) n (%)	Mean difference (%)
Treatment discontinuations						
Discontinued for reasons other than death	696 (23.2%)	699 (23.3%)	-0.1%	444 (14.2%)	442 (14.1%)	0.1%
Any AE leading to treatment discontinuation	571 (19.1%)	551 (18.4)	0.7%	182 (5.8%)	181 (5.8)	0%
Serious/fatal AEs						
Any serious AE	1436 (47.9%)	1543 (51.6%)	-3.7%	1361 (43.5%)	1423 (45.5%)	-2%

Cardiac failure	448 (15.0%)	594 (19.9%)	-4.9%	262 (8.4%)	343 (11.0%)	-2.6%
Cardiac failure congestive	57 (1.9%)	66 (2.2%)	-0.3%	51 (1.6%)	73 (2.3%)	-0.7%
Acute myocardial infarction	50 (1.7%)	48 (1.6%)	0.1%	51 (1.6%)	58 (1.9%)	-0.3%
Atrial fibrillation	80 (2.7%)	92 (3.1%)	-0.4%	57 (1.8%)	47 (1.5%)	0.3%
Ischaemic stroke	42 (1.4%)	35 (1.2%)	0.2%	66 (2.1%)	60 (1.9%)	0.2%
Acute kidney injury	81 (2.7%)	107 (3.6%)	-0.9%	46 (1.5%)	50 (1.6%)	-0.1%
COVID-19	49 (1.6%)	47 (1.6%)	0%	165 (5.3%)	131 (4.2%)	1.1%
Pneumonia	100 (3.3%)	119 (4.0%)	-0.7%	97 (3.1%)	96 (3.1%)	0%
Chronic obstructive pulmonary disease	23 (0.8%)	37 (1.2%)	-0.4%	17 (0.5%)	16 (0.5%)	0%
Urinary tract infection	36 (1.2%)	28 (0.9%)	0.3%	30 (1.0%)	32 (1.0%)	0%
Hypoglycaemic events[a]	73 (2.4%)	78 (2.6%)	-0.2%	6 (0.2%)	7 (0.2%)	0%
Volume depletion events leading to discontinuation[b]	15 (0.5%)	9 (0.3%)	0.2%	42 (1.3%)	32 (1.0%)	0.3%
Death[c]	56 (1.9%)	38 (1.3%)	0.6%	36 (1.2%)	38 (1.2%)	0%
AE with outcome of death	287 (9.6%)	297 (9.9%)	-0.3%	507 (16.2%)	529 (16.9%)	-0.7%
AEs of any severity						
Ketoacidosis	4 (0.1%)	5 (0.2%)	-0.1%	2 (0.1%)	0 (0%)	0.1%

[a]The EAG notes that the definitions may not be aligned in the two trials but it has included this given it is an AESI noted in Table 29 of the CS – it is defined as hypoglycaemic AE with a plasma glucose value ≤70 mg/dL (or where assistance was required) in EMPEROR-Preserved and as any major hypoglycaemic event (where all following criteria were met: patient experienced symptoms of severe impairment in consciousness or behaviour, patient required external assistance, intervention was required to treat the hypoglycaemia and there was prompt recovery of acute symptoms following the intervention); [b]the EAG notes that definitions may not be aligned in the two trials but it has included this given it is an AESI noted in Table 29 of the CS – it is defined as volume depletion events leading to discontinuation in EMPEROR-Preserved and any serious AE or AE leading to discontinuation of treatment that was suggestive of volume depletion; [c]deaths not attributed to another preferred term by the investigator.

The population analysed in both trials for AEs was the safety analysis set or treated set, which refers to those randomised and that received at least one dose of intervention drug or placebo (analysed according to randomised groups).

The EAG has adapted Table 30 in the CS to add other AEs considered appropriate, based on those included as AESI in Table 29 of the CS or the economic modelling in TA902; not all of these could be added given data was not publicly available for the DELIVER trial.[1] Additional data was obtained from the CTR for EMPEROR-Preserved and DELIVER publication and supplementary material.[6, 7]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CS, company submission; CTR, clinical trial report; EAG, External Assessment Group.

Cost Comparison Appraisal

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 29 August** using the below comments table.

All factual errors will be highlighted in a report and presented to the Chair and lead team and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Section 3.1 Population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15: "In general, the EAG's clinical experts were not concerned that these differences would have a large impact on outcomes but noted that the difference between prior LVEF ≤40% inclusion **and the proportion using loop diuretics** might have some impact".	We propose to remove the phrase "**and the proportion using loop diuretics":** "In general, the EAG's clinical experts were not concerned that these differences would have a large impact on outcomes but noted that the difference between prior LVEF ≤40% inclusion might have some impact".	DELIVER allowed enrolment of stabilised (no longer requiring intravenous diuretics) patients actively or recently hospitalised for heart failure, which may suggest a greater degree of baseline congestion in the DELIVER population and hence greater proportion of loop diuretics use. Use of loop diuretics at baseline also suggests increase severity of HF and increase risk of HF events. However, there is evidence that use of empagliflozin and dapagliflozin is effective regardless of diuretic use and dose: a) In Emperor-Reduced, the benefits of empagliflozin did not differ among patients with and	Not factually inaccurate, no change required.

		without recent volume overload (Packer, 2021) b) In EMPEROR-Preserved, treatment with empagliflozin was similar regardless of diuretic use of dose (Butler, 2023) c) Dapagliflozin treatment vs placebo was consistent across wide range of diuretic categories and dose (Chatur, 2023). Although we understand the EAG is simply reporting what their clinical experts said, we believe the statement should be supported by evidence. If no evidence is available, can you please implement our proposed amendment or include our comments alongside the expert's comments.	

Issue 2 Section 3.2 Intervention

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15: “One of the EAG’s clinical experts noted that fewer patients are receiving loop diuretics (67.7% in both arms of EMPEROR-Preserved) **than would be expected** and that patients not taking these are more likely not to have genuine heart failure. They indicated that this might reduce the efficacy of empagliflozin slightly, particularly when compared to DELIVER as proportions are slightly higher in that trial, but that any impact on comparisons between empagliflozin and dapagliflozin would likely be small (see Appendix 9.3).”	We propose to change the statement in bold so that the statement reads: “One of the EAG’s clinical experts noted that fewer patients are receiving loop diuretics (67.7% in both arms of EMPEROR-Preserved) **than in the DELIVER trial** and that patients not taking these are more likely not to have genuine heart failure. They indicated that this might reduce the efficacy of empagliflozin slightly, particularly when compared to DELIVER as proportions are slightly higher in that trial, but that any impact on comparisons between empagliflozin and dapagliflozin would likely be small (see Appendix 9.3).”	We agree that in DELIVER a greater proportion of patients (87.7%) were on a loop diuretic. DELIVER included patients in both hospitalised and ambulatory settings. Therefore, these patients were more symptomatic based on NYHA functional class, which may suggest a greater degree of baseline congestion in the DELIVER population and hence greater proportion of loop diuretics use. However, the statement that the patients in EMPEROR-Preserved had made less use of loop diuretics than would be expected in this patient population is not correct. Data provided in two recent UK observational studies, show that in the HFpEF/HFmrEF population the use of loop diuretics ranges from 48% to	Not factually inaccurate, no change required.

		73% at most, and the use of loop diuretics in EMPEROR-Preserved is not outside this range (Dierckx, 2015) (Straw, 2023). Although we understand the EAG is simply reporting what their clinical experts said, we believe the statement should be supported by evidence. If no evidence is available, can you please implement our proposed amendment or include our comments alongside the expert's comments.	

Issue 3 Section 3.2 Intervention

Description of problem	Description of proposed amendments	Justification for amendment	EAG response
Page 15: "One of the EAG's clinical experts noted that fewer patients are receiving loop diuretics (67.7% in both	We propose to delete the statement we highlighted in bold so that the statement reads: "One of the EAG's clinical experts noted that fewer patients are receiving	Within the context of the whole paragraph, the statement that patients not taking diuretics are more likely not to have genuine	Not factually inaccurate, no change required.

arms of EMPEROR-Preserved) than would be expected **and that patients not taking these are more likely not to have genuine heart failure.** They indicated that this might reduce the efficacy of empagliflozin slightly, particularly when compared to DELIVER as proportions are slightly higher in that trial, but that any impact on comparisons between empagliflozin and dapagliflozin would likely be small (see Appendix **Error! Reference source not found.**)."	loop diuretics (67.7% in both arms of EMPEROR-Preserved) than would be expected. They indicated that this might reduce the efficacy of empagliflozin slightly, particularly when compared to DELIVER as proportions are slightly higher in that trial, but that any impact on comparisons between empagliflozin and dapagliflozin would likely be small (see Appendix **Error! Reference source not found.**)."	heart failure may imply that more patients in EMPEROR-Preserved are more likely not to have genuine heart failure. This implication does not reflect the fact that inclusion criteria for both EMPEROR-Preserved and DELIVER include: diagnosis of CHF, LVEF>40%, evidence of structural heart disease (or prior HHF in case of EMP-P), and elevated NT-ProBNP. The patients in the EMPEROR-Preserved trial were diagnosed with chronic HF with evidence of structural heart disease within 6 months of visit 1 or documented previous hospitalisation for HF within 12 months prior to visit 1, and evidence of elevated NT-proBNP. To suggest that this trial may have not included genuine	

		heart failure patients would not be accurate. Therefore, we believe that to prevent ambiguous and incorrect interpretation, the statement should be made more precise, as we have proposed. Although we understand the EAG is simply reporting what their clinical experts said, we believe the statement should be supported by evidence. If no evidence is available, can you please implement our proposed amendment or include our comments alongside the expert's comments.	

Issue 4 Section 4.2.2.1 HHF and mortality outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20:	The sentence should be modified to:	The HRs for AC vs. CV mortality in the EMPEROR-	The EAG thanks the company for noticing the

"There may be some signal from DELIVER that non-CV deaths are also increased in the dapagliflozin group compared to placebo in the HFpEF/HFmrEF population (as the point estimate of the HR for AC mortality is closer to 1.0 than the point estimate of the HR for CV mortality; 0.94 vs 0.88) but this is slightly less notable than the difference for EMPEROR-Preserved **(0.91 vs 1.00)."**	"There may be some signal from DELIVER that non-CV deaths are also increased in the dapagliflozin group compared to placebo in the HFpEF/HFmrEF population (as the point estimate of the HR for AC mortality is closer to 1.0 than the point estimate of the HR for CV mortality; 0.94 vs 0.88) but this is slightly less notable than the difference for EMPEROR-Preserved **(1.00 vs 0.91)**."	Preserved trial are the wrong way around (HR for AC mortality is 1.00 and HR for CV mortality is 0.91).	error, which has been amended in the EAG report.

Issue 5 Section 4.2.2.2 Quality of life – KCCQ

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 22: **"However**, the EAG notes that differences may not be clinically important, as a threshold of ≥5 points has been suggested as indicating clinically important	We propose to delete the word 'however' at the start of the paragraph and add the sentence in bold: "The EAG notes that differences may not be clinically important, as a threshold of ≥5 points has been suggested as indicating clinically important changes from baseline (and differences vs placebo	We believe that the EAG's statement should be expanded as we have proposed, in order to provide a more accurate context about the appropriate use of the 5-point threshold.	Not factually inaccurate, no change required.

changes from baseline (and differences vs placebo did not reach this)."	did not reach this). **However, it should be acknowledged that the 5-point threshold change has been identified as meaningful in individual patients rather than in populations of patients. In these studies, it may be difficult to achieve a 5-point between-group difference, especially if the baseline KCCQ score is >70, indicative of a reasonably good quality of life and health status (Butler, 2022)."**		

Issue 6 Section 4.3.3.2 KCCQ outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 35: "The EAG notes that results for both definitions mentioned above for empagliflozin are lower compared to results obtained for dapagliflozin (suggesting less of a benefit in terms of KCCQ score for empagliflozin). However, overall, the EAG considers that differences	We propose to delete the paragraph.	The magnitude of the treatment effect on KCCQ health status seen in the EMPEROR-Preserved trial may appear to be modest (1.0–2.0 points) compared with a change of 5.0 points, which is commonly regarded as representing a clinically meaningful shift in KCCQ scores. However, it should be noted that large between-group differences in KCCQ scores (e.g, 10- to 15-point treatment effects) have typically been observed only	Not factually inaccurate, no change required.

for both drugs vs placebo could be considered similar as they are both below the threshold usually considered to be a clinically important change for KCCQ outcomes (5-points, as mentioned in the EAG reports of the STAs for empagliflozin and dapagliflozin in this indication), which may suggest that neither of the treatments have a large impact on KCCQ score at the trial-level.”		in patients who were severely compromised at baseline and particularly in unblinded device trials, in which knowledge that a patient has received active therapy likely exaggerated changes in their perception of their own response to an experimental intervention. The magnitude of the treatment effect in EMPEROR-Preserved is similar to that seen in other large-scale double-blind trials of drug therapies, particularly in patients with HFpEF (e.g. TOPCAT and PARAGON-HF; DELIVER) (Butler, 2022). Can you please implement our proposed amendment or include our comments alongside the expert’s comments.	

Issue 7 Section 4.5 Conclusions of the clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46: "While the EAG used definitions and time-points that were as aligned as possible between the two trials for KCCQ outcomes, some bias favouring dapagliflozin may remain given **patients** that patients in DELIVER that had their 8-month follow-up after the date."	We believe there is a typing error. "While the EAG used definitions and time-points that were as aligned as possible between the two trials for KCCQ outcomes, some bias favouring dapagliflozin may remain given that patients in DELIVER that had their 8-month follow-up after the date."	Correction of typing error.	The EAG thanks the company for noticing the error, which has been amended in the EAG report.

Issue 8 Appendix 9.2 EAG's critique of the SLR. Table 10 A summary of the EAG's critique of the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57: "The EAG is unsure whether switching from	We suggest to remove this statement.	Our proposed amendment is supported by the study by Fortier 2013, which states that "*there are no notable difference between Ovid and*	The EAG thanks the company for the additional information by

searching MEDLINE and Embase via Embase.com to using Ovid to search these databases would impact retrieval."		*Embase.com in terms of search results when searching Embase and Medline"*. Further, the same methodological approach was followed in HFrEF submission and was deemed acceptable.	Fortier 2013 and has made the requested amendment.

Issue 9 Appendix 9.2 EAG's critique of the SLR. Table 10 A summary of the EAG's critique of the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58: "The EAG considers the reporting of methods for screening to be adequate **but is unsure what impact the change in screening method for the most recent update could have on included studies**."	We suggest to delete the statement in bold, so that the statement reads: "The EAG considers the reporting of methods for screening to be adequate."	The statement is not supported by the published literature on this topic, which demonstrated that the implementation of this change in screening method in the last update is expected to have minimal to low impact on the risk of missing any relevant studies (Smela, 2020; Taieb 2018). Further, in this case, the software was trained from a total of four updates spanning thousands or publications; therefore, a very large number of screened studies was used by the DistillerSR program to inform its selection algorithm, hence minimising even further the risk of excluding any relevant studies.	The EAG thanks the company for the additional information by Smela 2020 and Taieb 2018, and has made the requested amendment.

		Published studies support the conclusion that a very low rate of discordance would be expected with the use of DistillerSR supporting as a second reviewer which has been shown to be comparable to a human reviewer (Smela, 2020; Taieb 2018).	

Issue 10 Appendix 9.2 EAG's critique of the SLR. Table 10 A summary of the EAG's critique of the SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58: "The EAG agrees with the company's reasoning in Table 9 of the CS when explaining why only EMPEROR-Preserved was included for empagliflozin in this CCA **were not included as part of this CCA**"	We are unable to propose an amendment because this sentence has unclear meaning. It seems that some information is missing before the statement in bold.	Possible typing error.	The EAG thanks the company for noticing the error. The sentence has been amended to, "*The EAG agrees with the company's reasoning in Table 9 of the CS when explaining why only EMPEROR-Preserved was included for empagliflozin in this CCA*"

Issue 11 Appendix 9.3 Comparison of baseline characteristics, standard care of treatments and study design in EMPEROR-Preserved and DELIVER trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59: "One clinical expert noted that the proportions using	We propose to delete the paragraph.	Please see our arguments in Issues 1 to 3 above.	Not factually inaccurate, no change required.

loop diuretics is low in both trials compared to what would be expected in UK clinical practice; as patients not using these are more likely *not* to have genuine heart failure and the efficacy of treatments might subsequently be reduced in these patients, and the proportion using them is lower in EMPEROR-Preserved, this may have reduced the efficacy of empagliflozin slightly compared to dapagliflozin in any ITCs."			

Issue 12 Appendix 9.3 Comparison of baseline characteristics, standard care of treatments and study design in EMPEROR-Preserved and DELIVER trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59: "Some of these differences suggest that the DELIVER trial may be	The sentence should be modified to: "Some of these differences suggest that the DELIVER trial may be a sicker population (higher proportions in	The DELIVER trial includes a lower proportion of LVEF ≥60% than EMPEROR-	The EAG thanks the company for noticing the error, which has been

a sicker population (higher proportions in DELIVER with NYHA class III, lower proportions with LVEF **≤60%** and more patients with atrial fibrillation or flutter)"	DELIVER with NYHA class III, lower proportions with LVEF **≥ 60%** and more patients with atrial fibrillation or flutter)"	Preserved trial (see Table 23 in the CS).	amended in the EAG report.

Issue 13 Appendix 9.3 Table 11. Comparison of baseline patient characteristics between EMPEROR-Preserved and DELIVER

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 61: For some of the variables the statistical unit (e.g. 'n' or '%') is not specified.	Please specify the statistical unit used in relation to each of the variables in Table 11.	For easy reading of the table.	The units have been added as requested.

Issue 14 Appendix 9.3 Table 11. Comparison of baseline patient characteristics between EMPEROR-Preserved and DELIVER

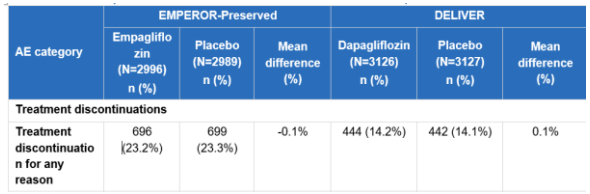
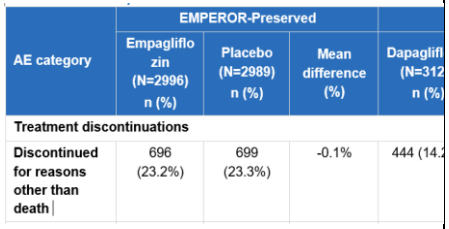
<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Page 61:

The data for ACEI/ARB for empagliflozin incorrectly reported to be 82.8% vs placebo is 82.5%. The current data in Table 11 is reported below:

<table>
<tr><th rowspan="2">Baseline characteristic</th><th colspan="2">EMPEROR-Preserved</th></tr>
<tr><th>Empagliflozin (N=2997)</th><th>Placebo (N=2991)</th></tr>
<tr><td>ACEI</td><td>1199 (40.0)</td><td>1210 (40.5)</td></tr>
<tr><td>ACEI/ARB</td><td>2481 (82.8)</td><td>2467 (82.5)</td></tr>
<tr><td>ARB</td><td>1177 (39.3)</td><td>1139 (38.1)</td></tr>
</table>
</td>
<td>Please correct the data for ACEI/ARB in Table 11 as detailed below:

<table>
<tr><th rowspan="2">Baseline characteristic</th><th colspan="2">EMPEROR-Preserved</th></tr>
<tr><th>Empagliflozin (N=2997)</th><th>Placebo (N=2991)</th></tr>
<tr><td>ACEI</td><td>1199 (40.0)</td><td>1210 (40.5)</td></tr>
<tr><td>ACEI/ARB</td><td>2367 (79.0)</td><td>2338 (78.2)</td></tr>
<tr><td>ARB</td><td>1177 (39.3)</td><td>1139 (38.1)</td></tr>
</table>
</td>
<td>The source of data used by the EAG for ACEI/ARB was Table 15.1.1:14 in the CTR (Drugs used at baseline or at any time up to end of planned treatment period). However, the correct source of data is Table 15.1.1:13 (Drugs used at baseline. Please see below)
  </td>
<td>The EAG thanks the company for noticing the error, which has been amended in the EAG report.</td>
</tr>
</table>

Issue 15 Appendix 9.3 Table 13. Summary of AEs in EMPEROR-Preserved and DELIVER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 63: 	Please correct the variable name from "**Treatment discontinuation for any reason"** to "**Discontinued for reasons other than death"**. 	We could not find the data for "Treatment discontinuation for any reason", but we could find the corresponding data in "Discontinued for reasons other than death" in both EMPEROR-Preserved and DELIVER trial. According to EMPEROR-Preserved trial, the trial medication was stopped for *reasons other than death* in 696 patients (23.2%) receiving empagliflozin and in 699 patients (23.4%) receiving placebo (Anker, 2021). According to DELIVER trial, this data is listed in results as: '*Dapagliflozin was discontinued for reasons other than death* in 444 patients (14.2%), and placebo was discontinued for reasons other than death in 442 patients (14.1%)'.	The EAG thanks the company for noticing the error, which has been amended in the EAG report.

AE category	EMPEROR-Preserved			DELIVER		
	Empagliflozin (N=2996) n (%)	Placebo (N=2989) n (%)	Mean difference (%)	Dapagliflozin (N=3126) n (%)	Placebo (N=3127) n (%)	Mean difference (%)
Treatment discontinuations						
Treatment discontinuation for any reason	696 (23.2%)	699 (23.3%)	-0.1%	444 (14.2%)	442 (14.1%)	0.1%

AE category	EMPEROR-Preserved			
	Empagliflozin (N=2996) n (%)	Placebo (N=2989) n (%)	Mean difference (%)	Dapagliflozin (N=312 n (%)
Treatment discontinuations				
Discontinued for reasons other than death	696 (23.2%)	699 (23.3%)	-0.1%	444 (14.2

		It should be noted that the discontinuation rate was similar between medication and placebo arm in both trials.	

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Section 4.2.2.1 HHF and mortality outcomes, Page 20: "while empagliflozin appears to [redacted] CV death from [redacted] (**Error! Reference source not found.**), there appears to be a [redacted] on non-CV death, which starts [redacted] [redacted] (**Error! Reference source not found.**). The proportion of patients with non-CV death events was [redacted]	Can you please also mark the word "[redacted]" as academic in confidence.	"while empagliflozin appears to [redacted] CV death from [redacted] (**Error! Reference source not found.**), there appears to be a [redacted] on non-CV death, which starts [redacted] [redacted] (**Error! Reference source not found.**). The proportion of patients with non-CV death events was [redacted] for empagliflozin and [redacted] for placebo."	Confidential marking has been amended as suggested.

for empagliflozin and [redacted] for placebo."			
Section 4.2.2.4 Subgroups, Page 23: "the most notable difference was between [redacted]); however, the EAG acknowledges that the NYHA class III/IV group is much smaller than NYHA class I/II"	Please mark the phrase "the NYHA class III/IV group is much smaller than NYHA class I/II" as academic in confidence as it reveals that the difference detected was in relation to this outcome.	"the most notable difference was between [redacted]); however, the EAG acknowledges that [redacted]"	

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