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

Technology appraisal committee C 17 January 2023

Chair: Steve O'Brien

Public handouts.
Contains no AIC or CIC information.

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Companies: AstraZeneca (dapagliflozin), Boehringer Ingelheim (empagliflozin)

Abbreviations

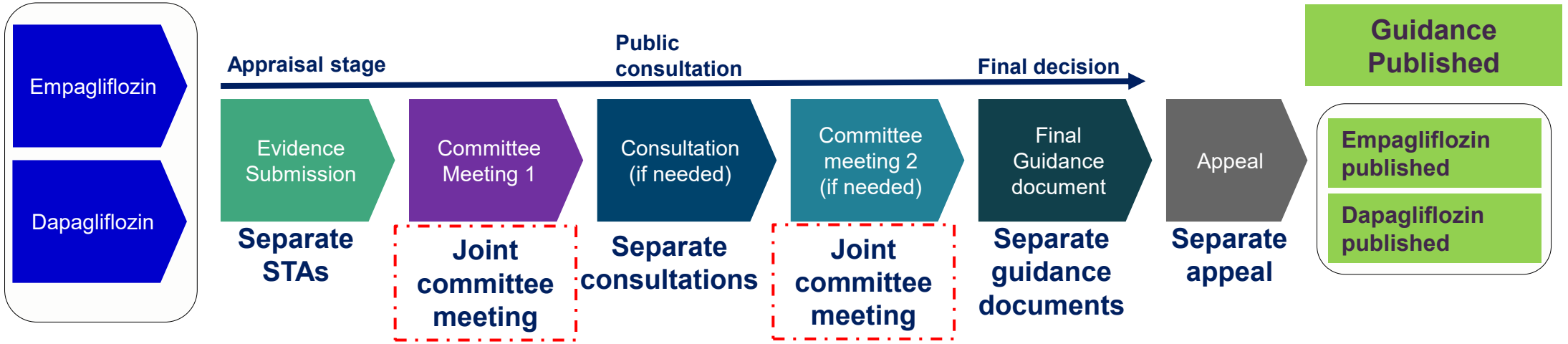
AE	Adverse event
CI	Confidence interval
CV	Cardiovascular
DSA	Deterministic sensitivity analysis
EAG	External Assessment Group
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
HF	Heart failure
HFimpEF	Heart failure with an improved ejection fraction
HFmrEF	Heart failure with a mildly reduced ejection fraction
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with a reduced ejection fraction
HHF	Hospitalisation for heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
KM	Kaplan-Meier
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
NHB	Net health benefit
NYHA	New York Heart Association
PSA	Probabilistic sensitivity analysis
SGLT2i	Sodium-glucose-co-transporter-2 inhibitor
SoC	Standard of care
T2DM	Type 2 diabetes mellitus

Pair appraisals pilot - introduction

Concept

Appraisals pipeline contains topics in same disease area that are likely to be evaluated at similar times.

- Two regular STAs, following STA principles
- Build on **efficiencies and economies of scale by aligning topics and sharing parts of the process** including internal and external aspects (NICE technical team, experts, EAG and committee discussion) to ensure alignment and reduce effort needed
- NICE is not comparing empagliflozin with dapagliflozin



NICE

EAG, evidence assessment group; STA, single technology appraisal

Background on chronic heart failure (cHF)

Heart failure is a common condition, associated with a high comorbidity burden and high mortality rates

Definition

- Inability of the heart to supply sufficient blood flow to meet the body's needs

Causes

- Abnormal functioning or structure of the heart due to certain conditions, such as ischaemic heart disease and hypertension

Epidemiology

- More than 500,000 people in England have heart failure
    - Around half of the people have **preserved or mildly reduced ventricular ejection fraction**
- Both prevalence and incidence increase with age

Symptoms

- Include difficulty breathing, fatigue, and ankle swelling

Prognosis

- 5-year survival for heart failure with preserved ejection fraction following hospitalisation is 35%
- Comorbidities, such as hypertension, and chronic kidney disease, are common, and associated with increased number of hospitalisation and risk of death

cHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction

Classification of chronic heart failure (cHF)

Left ventricular ejection fraction (LVEF)

Left ventricular ejection fraction (LVEF): Fraction of blood pumped by the left ventricle at each heart contraction, this is used to categorise the disease

Definitions of heart failure

LVEF	Categorisation	Treatment
40% or less	Heart failure with **reduced** ejection fraction (HFrEF)	Not relevant population for this appraisal Dapagliflozin (TA679) and empagliflozin (TA773) are both recommended by NICE in this population
41% to 49%	Heart failure with **mildly reduced** ejection fraction (HFmrEF)	Population of interest for this appraisal
50% or more	Heart failure with **preserved** ejection fraction (HFpEF)	Population of interest for this appraisal
Previously diagnosed HFrEF (LVEF ≤40%) which has now become HFpEF or HFmrEF (LVEF >40%)	Heart failure with **improved** ejection fraction (HFimpEF)	Population of interest for this appraisal – included in dapagliflozin trial

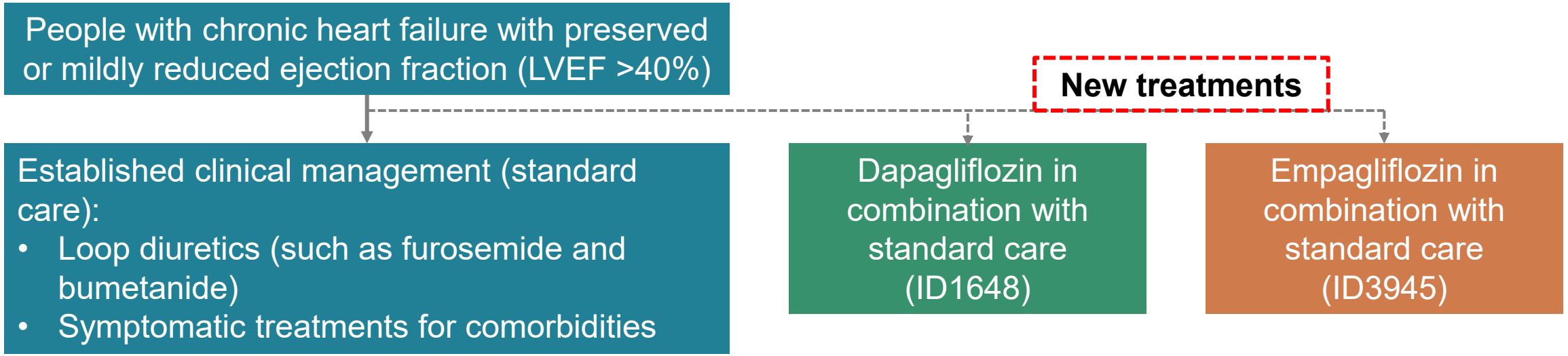
Source: 2021 European Society of Cardiology (ESC) guidelines

cHF, chronic heart failure; LVEF, left ventricular ejection fraction

Treatment pathway

No disease-modifying treatments for chronic heart failure with LVEF >40%

Treatment pathway for chronic heart failure with preserved or mildly reduced ejection fraction (LVEF >40%)



Does this treatment pathway reflect clinical practice? Is current clinical management given in primary or secondary care?

LVEF, left ventricular ejection fraction

Patient perspectives

Substantial unmet need for people with HFmrEF and HFpEF

Pumping Marvellous Foundation:

- No guidelines or prognostically beneficial treatments for people with HFpEF
  - Unacceptable and the largest unmet need
- Access to heart failure nurses and specialist multidisciplinary team services limited
- Lack of commissioned services for HFpEF because of the lack of evidence
- People with HFpEF usually prescribed diuretic for symptom relief and referred to primary care
  - Primary care not currently placed to treat people with HFpEF
- But GPs are familiar with prescribing SGLT2i for type 2 diabetes (T2DM)
  - May not need specialist reassessment when prescribing SGLT2i in primary care for HFpEF

We all believe more treatments need to be available for HFpEF patients

Patients feel they are left to wallow with nobody understanding how to help them

Patient cohort for HFpEF is significant. [Similar numbers] in cancer would cause a national outrage

NICE

GP, general practitioner; HFpEF, heart failure with preserved ejection fraction; SGLT2i, sodium glucose co-transporter 2 inhibitor

Clinical perspectives

Substantial unmet need for people with HFmrEF and HFpEF

UK Clinical Pharmacy Association – Heart Failure Committee:

- HFmrEF and HFpEF population is large with poor quality of life (QoL) and survival
- No treatment available with evidence of reduction in hospitalisation and CV death
- A clinically significant treatment response would be:
  - 20% reduction in hospital admission and CV deaths
  - Improved QoL and kidney function

Little existing technology for treating patients with an ejection fraction >40% other than diuretics and the management of comorbidities

British Cardiovascular Society – Clinical expert:

- SGLT2i already used within the NHS so could be adapted safely and rapidly
- Resource implication balanced by reduction in hospital admission and QoL benefits
- Meaningful clinical outcome means this a step change in management of HFpEF

Clinical expert:

- HF is a common cause of hospitalisation in >65 year old, treatment to reduce this would be welcome
- Will be used in specialist care, primary and secondary care following recommendation from a HF specialist

The SGLT2is are the first medications to offer a reduction in HF hospitalisation, which has a huge impact on patient care and the NHS

NICE

CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; QoL, quality of life; SGLT2i, sodium glucose co-transporter 2

Dapagliflozin (Forxiga, AstraZeneca) and empagliflozin (Jardiance, Boehringer Ingelheim)

Technology details for dapagliflozin and empagliflozin

	Dapagliflozin (ID1648)	Empagliflozin (ID3945)
Marketing authorisation	• Adults for the treatment of symptomatic chronic heart failure • Marketing authorisation granted by MHRA in December 2022 • Dapagliflozin is already recommended by NICE for treating chronic heart failure with reduced ejection fraction (TA679)	• Adults for the treatment of symptomatic chronic heart failure • Marketing authorisation granted by MHRA in June 2022 • Empagliflozin is already recommended by NICE for treating chronic heart failure with reduced ejection fraction (TA773)
Mechanism of action	• Highly potent, selective and reversible sodium-glucose co-transporter 2 (SGLT2) inhibitor • Inhibition reduces renal reabsorption of glucose and sodium in the kidney • Mechanism of action in chronic heart failure not yet fully understood	
Administration	Oral	
Price	• List price: £36.59 per pack of 28 x 10 mg tablets • List price: £477.30 per year of treatment • No patient access scheme	• List price: £36.59 per pack of 28 x 10 mg tablets • List price: £477.30 per year of treatment • No patient access scheme

NICE

EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Agency Regulatory Agency;

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Dapagliflozin	Empagliflozin	EAG comments
Population	Adults with symptomatic chronic heart failure with LVEF ≥40%	Adults with symptomatic chronic heart failure with LVEF >40%		Minor discrepancy, note indication for TA679 and TA779 of LVEF ≤40%
Intervention	Dapagliflozin + SoC Empagliflozin + SoC	Same as NICE scope		No comments
Comparators	Established clinical management, including but not limited to loop diuretics and symptomatic treatments for comorbidities	SoC (comprising loop diuretics, primarily furosemide or bumetanide)	SoC (comprising loop diuretics, sacubitril valsartan, ACEis, beta-blockers, ARBs and MRAs)	**Empagliflozin:** Sacubitril not appropriate comparator, but negligible impact on ICER
Outcomes	Symptoms of HF, hospitalisation for HF, all-cause hospitalisation, mortality, cardiovascular mortality, kidney function, adverse effects, HRQoL	Same as NICE scope		No comments

HF, heart failure; HRQoL, health-related quality of life; LVEF, left ventricular ejection fraction; SoC, standard of care

Key issues for dapagliflozin

Key issues

No.	Issue	Similar issue in ID3945?	ICER impact
4	Is dapagliflozin likely to have an impact on CV and overall mortality, and should this impact be captured in the model?	Yes	Large
3	What is the most appropriate extrapolation for estimating survival?	Yes	Small
1	Should amputation be included as an adverse event (AE) in the model?	No	Small
2	Do the annual AE probabilities lack external validity? Should annual AE probabilities from TA679 be considered?	No	Small
5	What are the appropriate NHS reference costs for non-elective care, given the potential impact of COVID-19? Are the inflation-adjusted 2019/2020 costs appropriate?	No	Small
6	What is the most appropriate resource use estimate for HHF events?	Yes	Small
-	Should initiation of dapagliflozin require advice from a HF specialist, or can it be initiated in primary care?	Yes	N/A
-	Impact of potential imputation of KCCQ-TSS transition probabilities	Yes	**Resolved**

NICE Note that the key issue number is from the EAG report

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio

Key issues for empagliflozin

Key issues

	Issue	Similar issue in ID1648?	ICER impact
4	Is empagliflozin likely to have an impact on CV and overall mortality and should this impact be captured in the model?	Yes	Large
1	Should LOCF imputation be used to estimate KCCQ-CSS transition probabilities?	No (resolved)	Large
2	Is empagliflozin likely to have a sustained, long-term treatment effect?	Yes*	Large
3	Is it appropriate to assume constant risk of HHF over time?	Yes*	Unknown
5	How long will a HHF event impact on QoL?	No	Large
6	What is the most appropriate resource use estimate for HHF events? What is the most appropriate cost for CV deaths?	Yes	Small
-	Should initiation of empagliflozin require advice from a HF specialist, or can it be initiated in primary care?	Yes	N/A

Note that the key issue number is from the EAG report.
*NICE team considers that this issue may also be relevant for dapagliflozin (ID1648)

NICE

CV, cardiovascular; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; LOCF, last observation carried forward; QoL, quality of life

Clinical effectiveness

Dapagliflozin (ID1648)

Key clinical trial: DELIVER

Clinical trial designs and outcomes

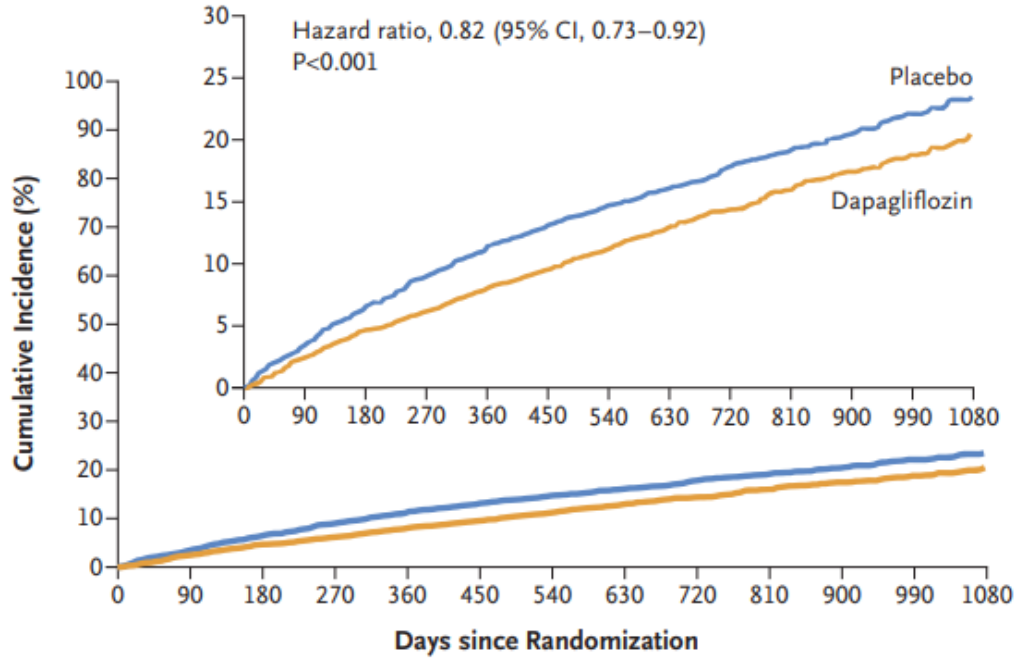
	DELIVER (NCT03619213)
Design	International, phase 3, randomised, double-blind, placebo-controlled trial
Population	Adults (≥40 years) with chronic HF NYHA class II-IV and EF >40%, with or without diabetes (N=6,263)
Intervention	Dapagliflozin, 10 mg taken orally once daily, plus standard of care
Comparator(s)	Placebo plus standard of care
Duration	Event-driven (anticipated duration 39 months), median time in study until primary analysis censoring date was [redacted] months. Study completion date: March 2022
Primary outcome	Time to first event of CV death or HF events (hospitalisation due to heart failure [HHF] or urgent heart failure visit [UHFV])
Key secondary outcomes	Total number of HF events and CV deaths; time to CV death; time to all-cause deaths; adverse events; PRO measured by KCCQ; EQ-5D-5L
Locations	20 countries, including in Europe, Asia, Latin America and North America; no UK patients
Used in model?	Yes

CSS, clinical summary score; CV, cardiovascular; EF, ejection fraction; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; HF, heart failure; HHF, hospitalisation due to heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; QoL, quality of life; NYHA, New York Heart Association;

DELIVER results: Primary outcome

Dapagliflozin reduced combined risk of CV death or HF event compared with placebo

Primary outcome: Composite outcome of CV death or HF event



Key primary and secondary outcomes

Key outcomes	HR (95% CI)
Primary outcome: Composite outcome of CV death or HF event	0.82 (0.73 to 0.92); p<0.001
Composite outcome of CV death or total (first and recurrent) HF events	RR 0.77 (0.67 to 0.89); p<0.001
Recurrent HF events	RR 0.73 (0.62 to 0.87); p=0.0003)
Change in mean KCCQ-TSS at 8 months	Point estimate: +2.4 (1.5, 3.3); p<0.001

NICE

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; RR, relative risk

DELIVER Kaplan-Meier survival curves

Dapagliflozin did not significantly reduce all-cause or CV mortality

***KM curves for all-cause deaths in DELIVER**
HR: 0.94; 95% CI: 0.83 to 1.07; p=0.3425

***KM curves for CV deaths in DELIVER**
HR: 0.88; 95% CI: 0.74 to 1.05; p=0.1678

*Curves from company model, shared by the EAG

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; KM, Kaplan-Meier

Clinical effectiveness

Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Key clinical trial: EMPEROR-Preserved

Clinical trial designs and outcomes

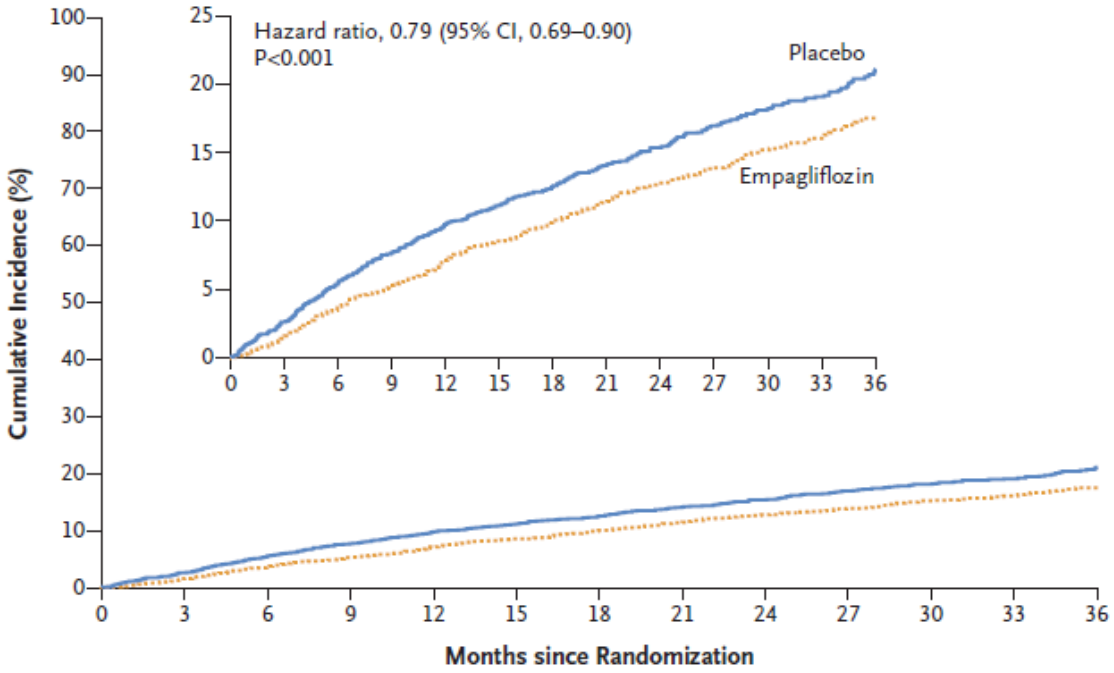
	EMPEROR-Preserved (NCT03057951)
Design	International, phase 3, randomised, double-blind, placebo-controlled trial
Population	Adults (≥18 years) with chronic HF NYHA class II-IV and EF >40%, with or without diabetes (N=5,988)
Intervention	Empagliflozin, 10 mg taken orally once daily, plus standard of care
Comparator(s)	Placebo plus standard of care
Duration	Event-driven, median follow-up 26.2 months. Study completion date: 26 April 2021
Primary outcome	Time to first event of adjudicated CV death or adjudicated hospitalisation due to heart failure (HHF)
Key secondary outcomes	HHF (first and recurrent); decline in renal function; time to first dialysis, renal transplant or sustained reduction of eGFR; time to first HHF; time to CV death; time to all-cause mortality; all-cause hospitalisation; adverse events; PRO measured by KCCQ; EQ-5D-5L
Locations	23 countries, including 25 patients randomised and treated in the UK
Used in model?	Yes

CV, cardiovascular; EF, ejection fraction; eGFR, estimate glomerular filtration rate; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; HF, heart failure; HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; PRO, patient-reported outcomes; QoL, quality of life;

EMPEROR-Preserved results (1/2)

Empagliflozin reduced combined risk of CV death or HHF compared with placebo

Primary outcome: Composite outcome of CV death or HHF



Key primary and secondary outcomes

Key outcomes	HR (95% CI)
Primary outcome: Composite outcome of CV death or HHF	**0.79 (0.69 to 0.90)**
Total number of HHF	**0.73 (0.61 to 0.88)**
Deterioration of renal function	**1.36 mL/min/1.73 m^2 per year (1.06 to 1.66); p<0.0001**
Time to composite renal outcome	0.95 (0.73 to 1.24); nominal p=0.7243
Time to first adjudicated HHF	**0.71 (0.60 to 0.83); nominal p<0.0001**
Time to onset of diabetes in people with pre-diabetes	0.84 (0.65 to 1.07); nominal p=0.15
First and recurrent all-cause hospitalisation	0.93 (0.85 to 1.01); nominal p=0.10

NICE

CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio

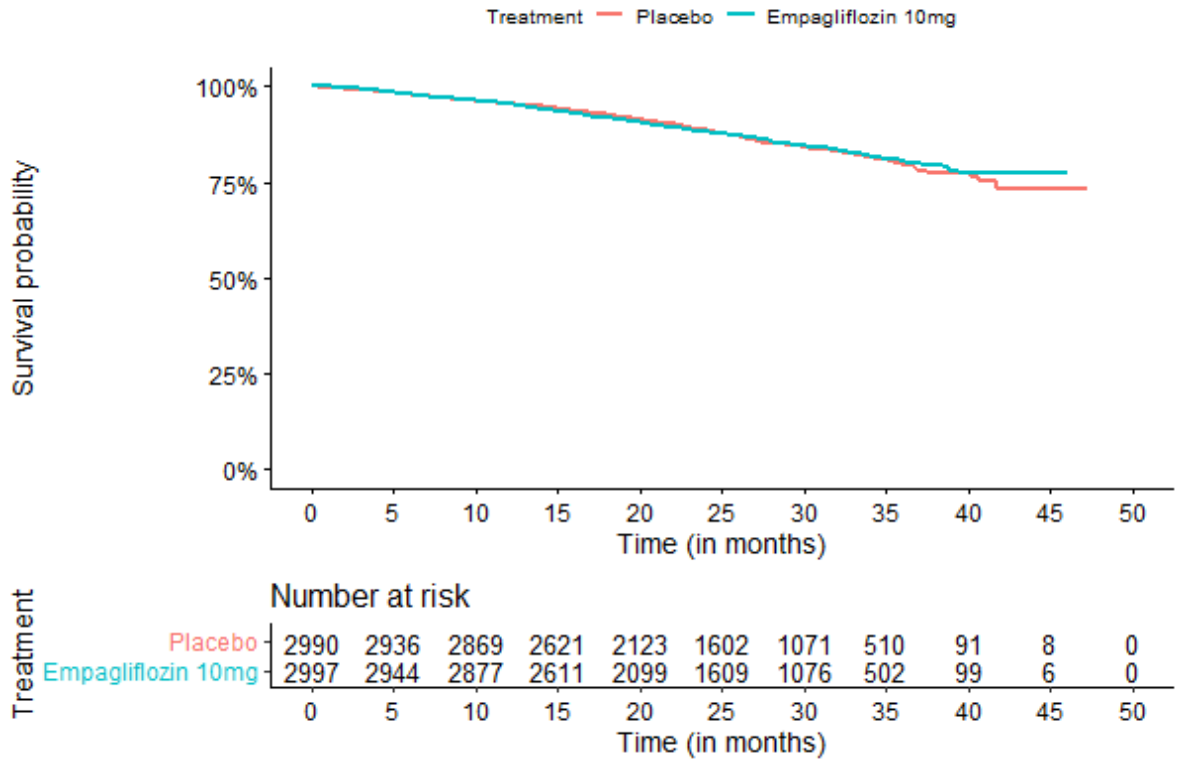
Outcomes in **bold** are statistically significant

EMPEROR-Preserved results (2/2)

Empagliflozin did not significantly reduce all-cause or CV mortality

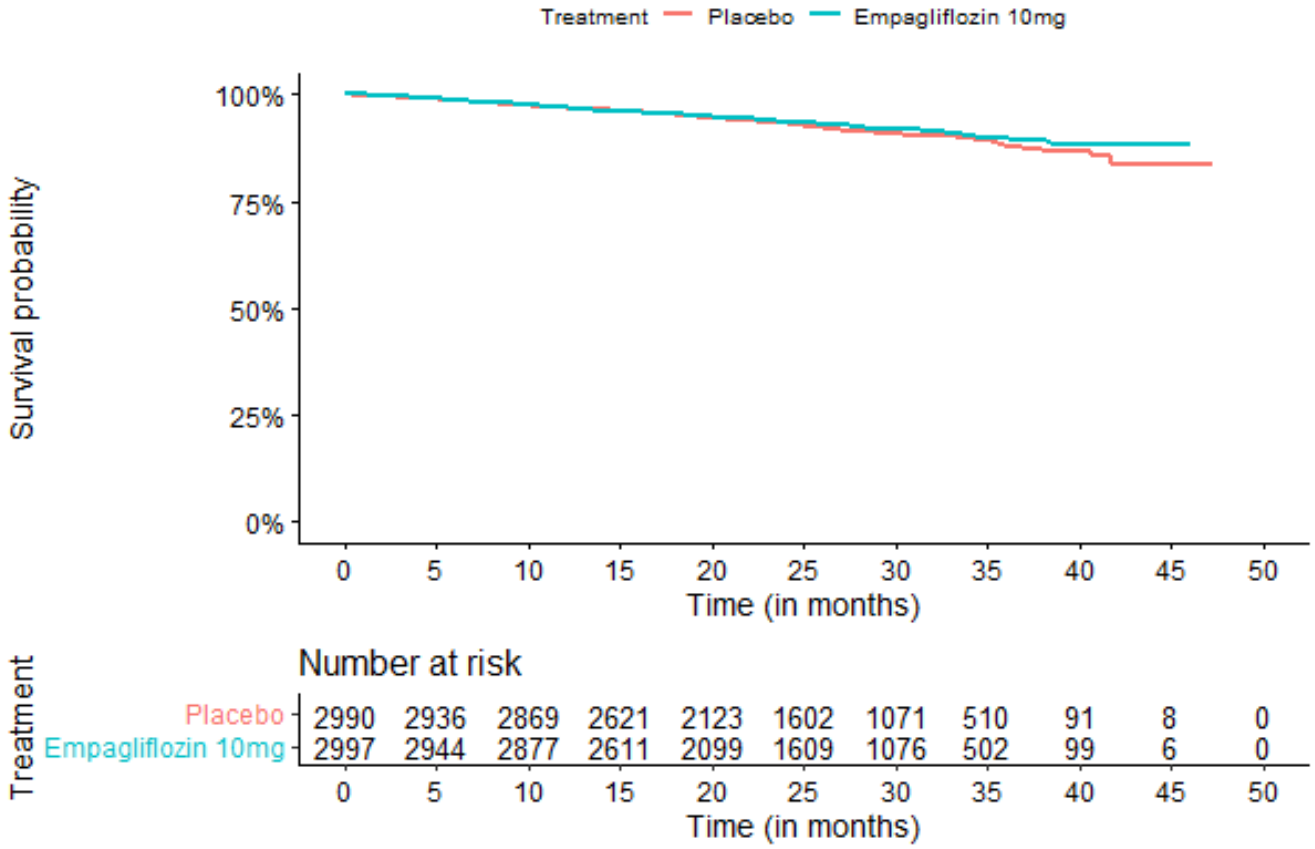
Observed OS data in EMPEROR-Preserved

HR: 1.00; 95% CI: 0.87 to 1.15



Observed CV mortality data in EMPEROR-Preserved

HR: 0.91, 95% CI: 0.76 to 1.09



NICE

CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio

Cost effectiveness

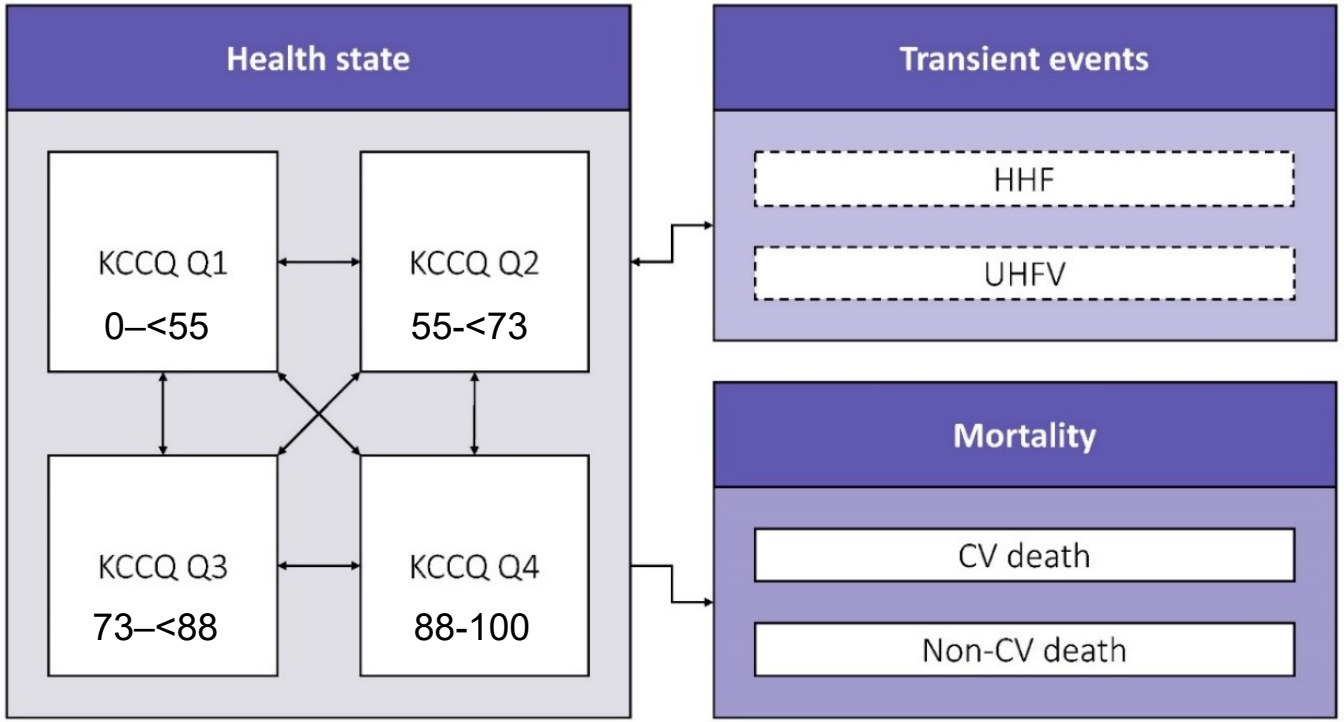
Dapagliflozin (ID1648)

Dapagliflozin: Company's model overview

- **Dapagliflozin** affects **costs** by:
  - Higher unit cost than SoC alone
  - **Decreasing** adverse events
  - **Decreasing** heart failure events (hospitalisation for heart failure [HHF] and urgent heart failure visits [UHFV])
  - **Decreasing** CV and all-cause mortality
- **Dapagliflozin** affects **QALYs** by:
  - **Increasing** proportion who stay in better KCCQ-TSS states, which leads to better quality of life, and indirectly leads to better survival and lower hospitalisation rates
  - **Decreasing** adverse events
  - **Decreasing** heart failure events (HHF and UHFV)
  - **Decreasing** CV and all-cause mortality
- Assumptions with greatest ICER effect:
  - Treatment effect on mortality
  - Treatment effect on heart failure events (HHF and UHFV)

KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; HF, heart failure; HHF, hospitalisation for heart failure; UHFV, urgent heart failure visits; CV, cardiovascular

Model structure: Markov model, health states defined by quartiles of baseline distribution of KCCQ-TSS, CV death and non-CV death



Used Kansas City Cardiomyopathy Questionnaire – total symptom score (**KCCQ-TSS**)

- A disease-specific, patient-reported, quality of life measurement with scores between 0-100
- Lower scores represent worse outcomes – more frequent and severe symptoms
- **Also used in the HFrEF appraisal (TA679)**

Dapagliflozin: Model structure

Model description

Model structure	Cohort Markov model, with health states defined by KCCQ-TSS quartiles.
Population	Adults with symptomatic chronic HF with preserved (HFpEF) or mildly reduced (HFmrEF) LVEF
Intervention	Dapagliflozin + SoC (weighted average of 80% furosemide and 20% bumetanide)
Comparators	SoC (weighted average of 80% furosemide and 20% bumetanide)
Time horizon	Lifetime horizon (to 101 years of age); starting age [redacted] years
Model cycle	One month, with half-cycle correction applied
Discount rates	3.5% per annum for costs, QALYs and life years.
Utility values	EQ-5D-5L mapped to 3L for each KCCQ-TSS quartile
Perspective	NHS and Personal Social Services (PSS)

NICE

EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; 3L, 3 levels; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; LVEF, left ventricular ejection fraction; QALY, quality-adjusted life year; SoC, standard of care

Dapagliflozin: How company incorporated evidence into model

Input	Assumption and evidence source	
	Company	EAG
Baseline characteristics	DELIVER (scenario with CPRD also included)	
Intervention and comparator efficacy	DELIVER used to inform KCCQ-TSS transition probabilities; separate probabilities for months 0-4 and months 5+	
Impact of dapagliflozin on survival and survival extrapolation	**All-cause deaths:** Direct and indirect treatment effect (via KCCQ-CSS residency) **CV deaths:** Direct and indirect treatment effect (via KCCQ-CSS residency) **CV and all-cause deaths:** Weibull (distribution adjusted)	**All-cause deaths:** Direct and indirect treatment effect; indirect treatment effect only; no treatment effect **CV-related deaths:** Direct and indirect treatment effect; indirect treatment effect only; no treatment effect
Discontinuation	Discontinuation rate from DELIVER. On discontinuation, transition probabilities for SoC arm were used	Noted that model structure leads to sustained treatment effect
Utilities	DELIVER EQ-5D-5L mapped to 3L for each KCCQ-TSS quartile	Age-adjusted; with KCCQ-TSS Q4 equalling general population
Cost and resource use	eMIT, BNF, PSSRU 2021, and NHS Reference Cost 2020/2021	NHS Reference Cost 2019/2020 inflated to 2020/2021
Adverse events	Decrements applied for AKI, fracture, volume depletion, UTI and amputation	Excludes amputation

BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; eMIT, electronic market information tool; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; PSSRU, Personal Social Services Research Unit; UTI, urinary tract infection

Dapagliflozin: Modelling of CV and all-cause mortality

Company base case assumes direct and indirect treatment effect on CV mortality and all-cause mortality

- Adjusted Weibull models were selected as base case distributions for all-cause and CV-related mortality
- The risk equations for all-cause and CV mortality were adjusted for treatment effect of dapagliflozin, KCCQ-TSS health state, age, gender, BMI, race, LVEF, NT-proBNP, SBP, T2DM, AFF, history of HHF and HF duration. Coefficients for dapagliflozin treatment effect and KCCQ-TSS health state shown below

EAG comments:

- No statistically significant difference between arms in CV or all-cause mortality in DELIVER
- **Direct** (via treatment effect and KCCQ occupancy) and **indirect** treatment effect (via KCCQ occupancy) implied in the company's modelling
- Scenario analysis conducted:
  - Including direct and indirect treatment effect
  - Including indirect treatment effect only
  - Excluding direct and indirect treatment effect

Coefficients for treatment effect and KCCQ-TSS health state for survival equations for CV and all-cause death (Weibull distribution, base case)

	CV mortality		All-cause mortality	
Parameter	Coefficient	p-value	Coefficient	p-value
Dapagliflozin treatment effect	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q1: Time ≤1 year	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q1: Time >1 year	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q2	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q3	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q4: Time ≤1 year	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-TSS Q4: Time >1 year	[redacted]	[redacted]	[redacted]	[redacted]

AFF, atrial fibrillation/flutter; BMI, body mass index; CV, cardiovascular; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire – total symptom score; HHF, hospitalisation for heart failure; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus

Key issue 4: Treatment effect on survival (1/2)

Dapagliflozin impact on CV and all-cause mortality unclear

ICER impact: Large

Background

- Dapagliflozin effect on **both** CV and all-cause mortality were included in company model base case
- In DELIVER, dapagliflozin reduced CV and all-cause mortality versus SoC but the difference was not significant
- Non-CV mortality = all-cause mortality – CV mortality. Non-CV mortality applied in model as maximum risk from general population (2017-2019 life tables) or from DELIVER
- For the primary outcome (CV mortality and HF events), [redacted] was observed between those with HFimpEF and those with LVEF consistently >40% (p-value for interaction = [redacted])

CV mortality and all-cause mortality in HFimpEF vs consistent LVEF >40%

HR (95% CI; p-value)	CV mortality	All-cause mortality
Overall FAS population	0.88 (0.74 to 1.05; p=[redacted])	0.94 (0.83 to 1.07; p=[redacted])
HFimpEF group	[redacted]	[redacted]
Consistent LVEF >40% group	[redacted]	[redacted]
*Interaction p-value	[redacted]	[redacted]

Previously diagnosed with HFrEF (LVEF ≤40%) but have now become HFpEF or HFmrEF (i.e., LVEF >40%)

*interaction for HFimpEF vs consistent LVEF >40%; FAS, full analysis set; HFimpEF, heart failure with an improved ejection fraction

Key issue 4: Treatment effect on survival (2/2)

Dapagliflozin impact on CV and all-cause mortality unclear

ICER impact: Large

Company

- EAG scenario request to exclude treatment effect on CV and all-cause mortality is inappropriate – uncertainty surrounding treatment effect has been captured within probabilistic sensitivity analysis
- Point estimate suggests a reduction in mortality, results would be statistically significant with more events

EAG comments

- Clinical experts considered that dapagliflozin has no real effect on CV or all-cause mortality, and biological mechanism for dapagliflozin to reduce CV mortality is uncertain

CV mortality

- Impact on CV mortality in DELIVER [redacted] – people who had prior HFrEF (LVEF ≤40%) but whose condition had improved (LVEF >40%)
  - In clinical practice, people with HFimpEF would be eligible for an SGLT2i when their LVEF was <40% (HFrEF) and would be unlikely to stop treatment when their LVEF increased to >40%
- [redacted] in CV mortality in people with a consistent LVEF >40%

All-cause mortality

- No statistically significant difference in all-cause mortality, should be no treatment effect on all-cause mortality

Assumptions vs company base case (direct and indirect treatment effect for both CV and all-cause mortality)

→ Assuming **direct and indirect treatment effect on CV mortality and only indirect treatment effect on all-cause mortality** increases the ICER markedly

→ Assuming **only indirect treatment effect on CV and all-cause mortality** also increases the ICER markedly

→ Assuming **no direct or indirect treatment effect on CV and all-cause mortality** increases the ICER further

Is dapagliflozin likely to have an impact on CV and all-cause mortality? Should this impact, if any, be captured in the model? Should people with HFimpEF be included in the modelled population?

Key issue 3: Survival extrapolation (1/2)

Company selected Weibull model to extrapolate survival beyond trial data

ICER impact: Small

Background

- To model survival, the company used a piecewise approach
- Applied parametric survival curves at the inflection point of both trial arms (at 1 year) to DELIVER data

Company

- Based on statistical, visual and clinical validation, Weibull model most plausible
- Gompertz too pessimistic
- Scenario using Gompertz model raised the ICER from £7,519 to £9,590
- External validation conducted with literature findings (Shahim et al. and Jones et al.)

Adjusted CV mortality DELIVER

Extrapolations include no application of general population mortality or non-CV mortality

Key issue 3: Survival extrapolation (2/2)

ICER impact: Small

For external validation, DELIVER data was compared with reports by Shahim et al. Both Weibull and Gompertz model fit real-world evidence at different timepoints

Adjusted all-cause mortality from DELIVER (placebo arm only) reweighted and compared to long term survival reported by Shahim et al.

EAG comments

- Weibull likely underestimates CV mortality (~[redacted]% of patients had not died due to CV mortality at 92 years old)
- Shahim et al. study aligns with Gompertz at year 5 but with Weibull at year 10 – this is inconsistent
- Poor fit may be due to extrapolating only part of the survival data (that is, inflection point, after 1 year)
  - Company did not respond to request for single fully parametric survival model
  - No clear clinical rationale for why an inflection point between trial arms would be expected

What is the most appropriate extrapolation for estimating survival?

Key issue 1: Amputation included as an AE in the model

Link between amputation and HF unclear

ICER impact: Small

Background

- Historically, a link between SGLT2i and amputation was suspected but a recent meta-analysis suggests no link
- Amputation is a known risk with T2DM, and people with T2DM can also use SGLT2is, such as dapagliflozin

	Number of patients with amputations in DELIVER (N=[redacted])	
	Dapagliflozin + SoC	Placebo + SoC
With T2DM	[redacted]	[redacted]
Without T2DM	[redacted]	[redacted]

EAG comments

- [redacted] in amputations in people without T2DM for between treatment arms in DELIVER
- In clinical practice, people with T2DM may be eligible for dapagliflozin regardless of their HF status
- Amputation may be confounding and not linked to HF
- EAG excluded amputation in its base case, leading to an increase in ICER from £7,519 to £8,538

Company

- AEs of greater than 1% included in the model
  - Amputation in DELIVER was [redacted] but was included in the model due to historical link between use of SGLT2is and increased risk of amputation
- DELIVER included people who had not had SGLT2i for at least 4 weeks before randomisation

Should amputation be included as an AE in the model?

T2DM, type 2 diabetes mellitus; SGLT2i, sodium-glucose-co-transporter-2 inhibitor; QoL, quality of life

Key issue 2: External validity of AE probabilities

AE probabilities different in trials for people with LVEF ≤40% vs >40%

ICER impact: Small

Background

- Lower AE probabilities reported in DELIVER than DAPA-HF
- DAPA-HF used for NICE TA679 (dapagliflozin in people with HFrEF [LVEF ≤40%])

***Mean annual probability of AEs (%)**

Adverse events	This appraisal		TA679	
	DELIVER (>40%LVEF)		DAPA-HF (≤40%LVEF)	
	Dapa + SoC	SoC	Dapa + SoC	SoC
AKI	[redacted]	[redacted]	NR	NR
Renal events	[redacted]	[redacted]	4.1%	4.7%
Amputations	[redacted]	[redacted]	0.3%	0.3%
Fractures	[redacted]	[redacted]	1.4%	1.4%
UTI	[redacted]	[redacted]	1.6%	1.5%
Volume depletion	[redacted]	[redacted]	5.0%	4.5%

* Converted to, and shown as percentage

EAG comments

- DELIVER data lacks external validity; AE probabilities for HFmrEF/HFpEF and HFrEF expected to be similar
- Some AE probabilities may be higher for HFmrEF/HFpEF as population is older (+5.4 years) with more comorbidities

Company

- Comparison of DELIVER ([redacted]) and DAPA-HF ([redacted]) inappropriate and introduces uncertainty
- Baseline characteristics different for both study populations
- Scenario using TA679 AE probabilities increased ICER by £916

Should AE probabilities from TA679 be considered?

AKI, acute kidney injury; HFmrEF, heart failure with a mildly reduced ejection fraction; HFpEF, heart failure with a preserved ejection fraction; UTI, urinary tract infection

Key issue 5: Non-elective care cost

Cost of non-elective care markedly increased in 2020/2021

ICER impact: Small

Background

- Unit cost for non-elective in-patient care valued using NHS Reference Cost (2020/2021)
- The cost used for adverse events requiring non-elective care (amputation, HHF, fracture) appears markedly in 2020/2021 higher than recent years

Examples of non-elective in-patient care costs in NHS reference costs in past 3 years

	2017/2018	2018/2019	2019/2020	2020/2021
Amputation	£11,592	£11,367	£12,694	£17,267
Difference versus previous data	-	-£224	£1,327	£4,573
HHF	£2,832	-	£3,092	£4,093
Difference versus previous data	-	-	£260*	£1,001

*versus 2017/2018 data

EAG comments

- Large differences in cost likely due to impact of COVID-19
- Explore scenario with 2019/2020 cost inflated to 2020/2021 values

Company

- Scenario with EAG preference increased the ICER from £7,519 to £8,161

What is the appropriate NHS Reference Cost for non-elective care, given the potential impact of COVID-19? Is the inflation-adjusted 2019/2020 cost appropriate?

HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio

Key issue 6: Resource use estimate for HHF events

Length of hospitalisation for HHF events is unclear, this affects the cost

ICER impact: Small

Background

- To estimate length of hospitalisation for HHF events, the company used a weighted average composed of severe (53-day hospital stay) and less severe (13-day hospital stay) HHF

EAG comments

- Clinical experts suggest length of hospitalisation for HHF in **HFpEF** population is 11 days
- Company declined request to provide results for HHF length of hospitalisation in DELIVER
- The EAG used the less severe HHF cost code (EB03E; 13-day hospital stay) in its base case

Company

- DELIVER not tailored for length of hospitalisation comparison, there are also regional differences
- NHS Reference Cost not specific for population with LVEF >40% but best available data
- Scenario using NHS cost code EB03E (13-day hospital stay) and with 2019/2020 cost inflated to 2020/2021 increases ICER from £7,519 to £8,466

Which resource use estimate is appropriate for hospitalisation for heart failure (HHF)?
Is length of hospitalisation correlated with ejection fraction?

HHF, hospitalisation for heart failure; HFpEF, heart failure with preserved ejection fraction

Cost effectiveness

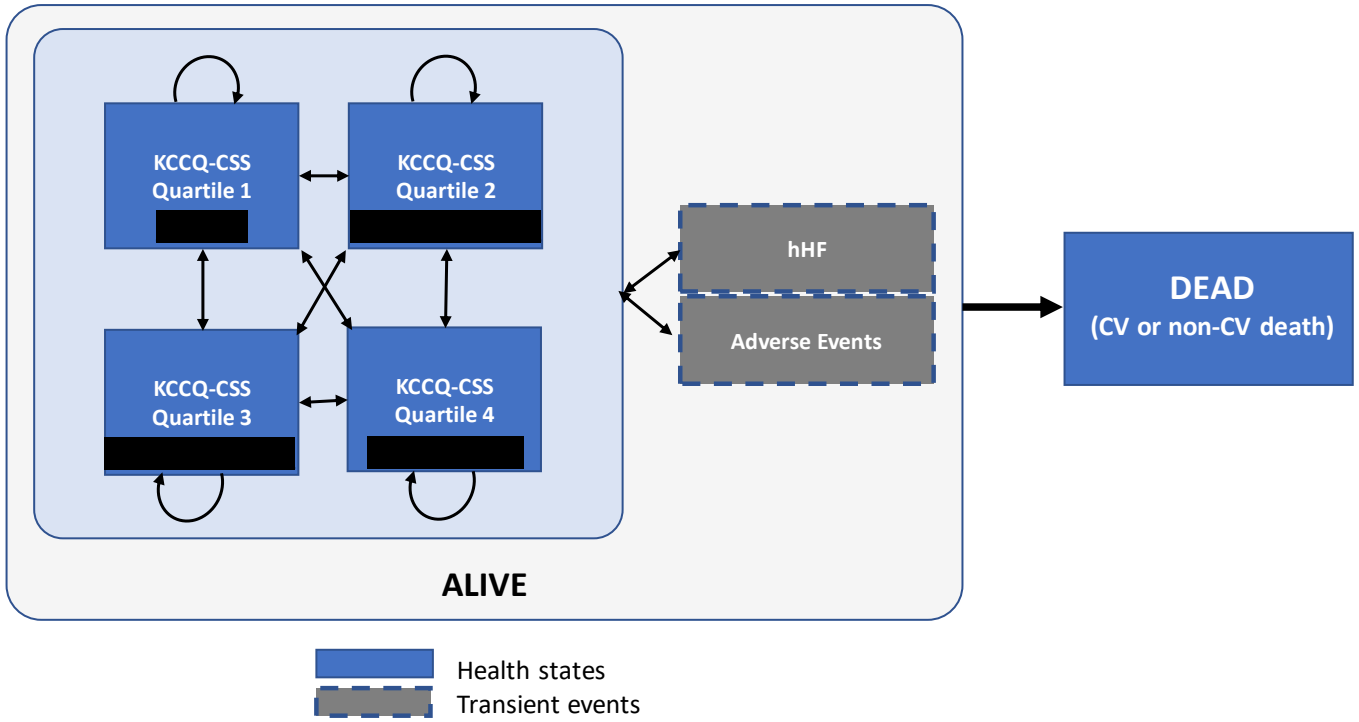
Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Empagliflozin: Company's model overview

- **Empagliflozin** affects **costs** by:
  - Higher unit cost than SoC alone
  - **Decreasing** hospitalisation for heart failure (HHF)
  - **Decreasing** CV deaths
- **Empagliflozin** affects **QALYs** by:
  - **Increasing** proportion who stay in better KCCQ-CSS states, which leads to better quality of life, and indirectly leads to better survival and lower hospitalisation rates
  - **Decreasing** hospitalisation for heart failure
  - **Decreasing** probability of death
- Assumptions that have the greatest effect on the ICER are:
  - Transition probabilities for distribution across KCCQ-CSS states
  - Impact of empagliflozin on survival
  - Duration of impact of HHF on quality of life

Model structure: Markov model, health states defined by quartiles of baseline distribution of KCCQ-CSS, and death



Used Kansas City Cardiomyopathy Questionnaire – clinical summary score (**KCCQ-CSS**)

- A disease-specific, patient-reported, quality of life measurement with scores between 0-100
- Lower scores represent worse outcomes – more frequent and severe symptoms
- **Also used in the HFrEF appraisal (TA773)**

NICE

CV, cardiovascular; HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; SoC, standard of care

Empagliflozin: Model structure

Model description

Model structure	Cohort Markov model, with health states defined by KCCQ-CSS quartiles.
Population	Adults with symptomatic chronic HF with preserved (HFpEF) or mildly reduced (HFmrEF) LVEF
Intervention	Empagliflozin + SoC (ARNIs, ACEIs, BBs, ARBs and MRAs)
Comparators	SoC (ARNIs, ACEIs, BBs, ARBs and MRAs)
Time horizon	Lifetime horizon; starting age 71.89 years
Model cycle	One month, with half cycle applied
Discount rates	3.5% per annum for costs and QALYs and life years.
Utility values	EQ-5D-5L mapped to 3L for each KCCQ-CSS quartile
Perspective	NHS and Personal Social Services (PSS)

NICE

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta-blockers; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; MRA, mineralocorticoid receptor antagonists; MRA, mineralocorticoid receptor antagonists; SoC, standard of care

Empagliflozin: How company incorporated evidence into model

Input	Assumption and evidence source	
	Company	EAG
Baseline characteristics	EMPEROR-Preserved Utility values from EMPEROR-Preserved with adjustment to general population norms	
Intervention and comparator efficacy	EMPEROR-Preserved used to inform KCCQ-CSS transition probabilities with LOCF imputation; separate probabilities for baseline to week 12, week 12 to 32 and week 32+	Used observed transition probabilities from EMPEROR-Preserved, rather than imputed values
Impact of empagliflozin on survival and survival extrapolation	**All-cause deaths:** Indirect treatment effect (via KCCQ-CSS residency) **CV deaths:** Direct and indirect treatment effect (via KCCQ-CSS residency) **All-cause and CV survival extrapolation:** Weibull	Scenarios explored: **All-cause deaths:** Direct and indirect treatment effect; Indirect treatment effect; no treatment effect **CV-related deaths:** Direct and indirect treatment effect; indirect treatment effect only; no treatment effect
Discontinuation	Discontinuation rate from EMPEROR-Preserved. On discontinuation, transition probabilities for SoC were used	Noted that model structure leads to sustained treatment effect. Additional scenarios conducted to explore this
Utilities	EQ-5D-5L from EMPEROR-Preserved, mapped to EQ-5D-3L Disutilities for HHF and AEs	Additional scenarios assess duration of HHF disutility
Cost and resource use	NHS and PSS price sources, and literature for other cost inputs	Updated cost of HHF event and CV death
Adverse events	Most common adverse events of special interest in EMPEROR-Preserved	

AE, adverse events; CV, cardiovascular; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – clinical summary score; EQ-5D-xL, EuroQol 5 Dimensions X Levels; HHF, hospitalisation for heart failure; LOCF, last observation carried forward PSSRU, Personal Social Services

Empagliflozin: Modelling of CV and all-cause mortality

Company base case assumes direct and indirect treatment effect on CV mortality, and indirect treatment effect on all-cause mortality

- Joint arm Weibull model was selected as base case distribution for all-cause and CV-related mortality
- The risk equations for all-cause and CV mortality are adjusted for treatment effect of empagliflozin (vs placebo) and of KCCQ-CSS health state (vs Q1). In the company's base case,
  - No direct treatment effect for all-cause mortality (treatment effect coefficient set to zero) → outcome not statistically significant in EMPEROR-Preserved and deemed to be clinically implausible
  - Direct treatment effect for CV mortality → outcome not statistically significant in EMPEROR-Preserved but deemed to be clinically **plausible**

EAG comments:

- Inclusion of KCCQ-CSS as predictor of survival generates an indirect survival benefit for empagliflozin, because people receiving empagliflozin are more likely to remain in better KCCQ-CSS states compared with people receiving SoC

Parametrisation of survival equations for all-cause and CV death (Weibull distribution, base case)

Parameter	All-cause death		CV death	
	Coefficients	p-value	Coefficients	p-value
Treatment effect of empagliflozin	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-CSS Q2	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-CSS Q3	[redacted]	[redacted]	[redacted]	[redacted]
KCCQ-CSS Q4	[redacted]	[redacted]	[redacted]	[redacted]

*In the company base case, this has been set to zero

NICE CV, cardiovascular; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – clinical summary score; SoC, standard of care

Key issue 4: Impact of empagliflozin on survival

Impact of empagliflozin on CV and all-cause mortality is unclear

ICER impact: Large

Background

- In trial, empagliflozin non-significantly reduced CV and overall mortality versus SoC
- In company base case, assumed an indirect treatment effect on all-cause mortality (via KCCQ-CSS residency) and a direct and indirect effect on CV mortality

EAG comments

- Not sufficient evidence from trial that empagliflozin has an impact on CV and overall mortality
- KCCQ-CSS should not be included in risk equation for all-cause mortality as this generates an indirect survival benefit for empagliflozin in model which is not supported by the trial data
- Unclear if treatment effect should be included in risk equation for CV mortality
  - Clinical expert opinion states that it is plausible that empagliflozin has an impact on CV mortality
- EAG base case assumes no impact of empagliflozin on overall survival

Is empagliflozin likely to reduce CV mortality compared to standard of care?

- **If yes,** does the impact of CV mortality translate into a reduction in overall mortality?
  - **No reduction in overall mortality** – people who don't die from CV cause die in a similar time frame from non-CV cause (due to age and comorbidities), and therefore more non-CV deaths for empagliflozin than standard of care arm
  - **Reduction in overall mortality** – people who don't die from CV cause die much later from non-CV cause and similar proportions of people die from non-CV causes in both arms in short-term
- **If no,** there is no difference in CV or non-CV deaths between empagliflozin and SoC

Key issue 1: Estimation of KCCQ-CSS transition probabilities

Unclear if use of LOCF imputation method appropriate

ICER impact: Large

Background

- Company uses last observation carried forward (LOCF) imputation method – assumes missing observation is identical to previous data point

Company

- Mean scores at weeks 12, 32 and 52 and distribution of KCCQ-CSS score change from baseline were similar between imputed and non-imputed datasets
- → Used LOCF approach, due to similarity between imputed and non-imputed scores

EAG comments

- Sufficient number of observations without imputations to provide a robust sample size
- Number of observations is similar across treatment arms, suggesting data are well balanced
- Use of LOCF method leads to plateau where observations are missing
- No data to validate the assumption that missing observations would be identical to previous data point, therefore more robust to use observed data without imputation
- Scenario analysis using observed data increases company's base case ICER from £14,429 to £20,198
- **EAG uses raw observed data for transition probabilities in base case**

The company uses LOCF imputation method, the EAG prefers use of raw observed KCCQ-CSS – which does the committee prefer?

ICER, incremental cost-effectiveness ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; LOCF, last observation carried forward

Key issue 2: Long-term effect on KCCQ-CSS (1/2)

Unclear if empagliflozin has sustained long-term treatment effect

ICER impact: Large

Background

- Company estimated transition probabilities between KCCQ-CSS quartiles from trial data for 3 periods (baseline to week 12; week 12 to 32; week 32 to 52)
  - Transition probabilities from last period (week 32+) used for rest of model time horizon
- On discontinuation of empagliflozin, transition probabilities for standard of care were used from then onwards

EAG comments

- Model structure gives sustained treatment effect over time – unlikely to be clinically plausible:
  - Low probability of moving health states from month 9+
  - At month 8, higher percentage of people receiving empagliflozin in highest KCCQ-CSS state (higher QoL)
  - Therefore, sustained treatment effect for patients discontinuing after month 8
- Assumption also impacts benefits with HHF and mortality, as these are dependent on distribution across KCCQ-CSS states
- **No change to EAG base case**

NICE team considers that this issue may also be relevant for dapagliflozin (ID1648)

HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QoL, quality of life

Key issue 2: Long-term effect on KCCQ-CSS (2/2)

Unclear if empagliflozin has sustained long-term treatment effect

ICER impact: Large

Company

- Explored uncertainty regarding waning of treatment effect in scenario analyses:

Company scenario analyses		ICER	EAG comments
Company base case		£14,429	
Set proportion of people in the KCCQ-CSS quartiles in empagliflozin arm equal to proportions in the SoC arm at 5, 3, 2 and 1 years	5 years	£16,139	**Lacks clinical plausibility.** Creates artificial drop in empagliflozin arm proportions, but then returns to respective transition probabilities for each treatment arm
	3 years	£17,187	
	2 years	£17,457	
	1 year	£16,985	
Transition probabilities between KCCQ-CSS quartiles for treatment arm are set to transition probabilities for SoC arm after 8 months		£32,482	**Likely to be overly pessimistic.** Empagliflozin stops working 8 months after patients initiate treatment (even for patients who carry on treatment for the rest of the model), and patients in empagliflozin catch up to SoC patients approximately 4 to 5 years after treatment initiation

Is empagliflozin likely to have a sustained, long-term treatment effect?

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QoL, quality of life; SoC, standard of care

Key issue 3: Estimation of HHF in the economic model

Unclear if appropriate to assume constant HHF hazard over time

ICER impact: Unknown

Background

- Used count data from EMPEROR-Preserved to model HHFs
- Monthly rate of HHFs estimated using Poisson model with time varying KCCQ-CSS states and treatment received as predictors
- Assumes constant risk of HHF and does not differentiate initial and subsequent hospitalisations

Company

- Poisson equation with time as a predictor was explored but had clinically implausible negative coefficient
- At clarification, fitted 6 distributions to time to first HHF event – most distributions showed decreasing or plateauing hazards, which are clinically implausible
- Subsequent hospitalisation analysis breaks randomisation

EAG comments

- More robust method for estimating HHF would be to use Kaplan-Meier data
  - Would have allowed extrapolation of HHF events over model time horizon
  - Would **not** have to assume constant rate of HHF
- EMPEROR-Preserved shows difference in empagliflozin's effect on first and subsequent hospitalisations
  - Difference across arms larger for first events ([redacted]) than for second events ([redacted])
  - Likely that empagliflozin does not have a benefit in preventing subsequent hospitalisations
  - By considering all events in trial as first events, model overestimates benefit of empagliflozin
  - Second HHF events occurred "faster" in relation to first HHF events
- Absolute number of HHF events in model are overestimated compared to trial data

EMPEROR-Preserved data

%	Empa	Placebo
1st HHF	8.6%	11.8%
2nd HHF	[redacted]	[redacted]

Is it appropriate to assume constant risk of HHF over time?

NICE team considers that this issue may also be relevant for dapagliflozin (ID1648)

Key issue 5: Duration of impact of HHF events on QoL

Duration of impact of HHF event on QoL is unclear

ICER impact: Large

Background

- Utility scores in model calculated using mixed-effect linear regression using EQ-5D from EMPEROR-Preserved
- Annual disutility for HHFs in model was [redacted] – calculated by multiplying the coefficients (estimated in the mixed-effects model) for time since HHF by the respective period of time and adding these together

Company

- HHFs in model impact QoL for 1 year after the event, aligned with assumption accepted by committee for TA679

EAG comments

- Disutility with HHF used higher than in TA773 (which was [redacted] per event)
- EAG clinical experts stated that duration of impact of HHF events on QoL was over-estimated
  - Average length of stay in hospital is 11 days (in EMPEROR-Preserved, mean stay for HHF was 11 days)
  - Experts stated that 1 day in hospital would impact QoL for 1 week after discharge, with maximum impact of 6 months after discharge.
  - EAG base case ranges between scenarios with duration of impact on QoL of 2.75 months and of 6 months

Duration of impact on QoL after discharge	ICER (£/QALY)
1 year (company base case)	£14,429
6 months	£16,511
2.75 months (11 weeks)	£17,912

How long will a HHF event impact on QoL?

EQ-5D, EuroQol 5 Dimensions; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; QoL, quality of life

Key issue 6: Costs of HHF events and CV deaths

ICER impact: Small

Uncertainty surrounding appropriate costs for HHF events and CV deaths

Company

- **Resource use for HHF events:** based on NHS reference costs for non-elective inpatient stay, weighted average of reference costs for HRG codes (EB03A to EB03E) and the number of finished consultant episodes
- **Cost of CV death:** based on regression analysis from Alva et al., estimated added inpatient costs for T2DM complications from study in England

EAG comments

Resource use for HHF events: Company over-estimates cost of HHF events

- Mean duration of HHF in EMPEROR-Preserved was 11 days (median: 8 days; Q3: 13 days)
- Company included more severe cost code (EB03A; 53-day hospital stay) in weighted average
- EAG preferred scenario using less severe cost code (EB03E; 13-day hospital stay)
- Small increase in ICER from £14,429 to £15,214

Cost of CV deaths: Company over-estimates costs of CV deaths

- Regression analysis from Alva et al. inappropriate as relate to added costs of hospitalisations due to T2DM complications – EAG prefer use of absolute cost of events in Alva et al.
- [redacted] of deaths in EMPEROR-Preserved were sudden cardiac death – EAG prefer conservative approach of assuming the cost of sudden cardiac death was £0
- Small increase in ICER from £14,429 to £14,854

What are most appropriate costs for HHF events and CV deaths?

Cost effectiveness results

Dapagliflozin (ID1648)

Dapagliflozin: Company base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£14,352	5.052	£1,885	0.251	£7,519	0.16	0.19
SoC	£12,467	4.801	-	-	-		

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£14,315	4.974	£1,896	0.261	£7,276	0.17	0.20
SoC	£12,419	4.714	-	-	-		

ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Dapagliflozin: Company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case	Inc. cost (EAG)	Inc. QALY (EAG)	ICER with EAG assumptions (£/QALY)	Cumulative ICER with EAG assumptions (£/QALY)
Company base case			£1,885	0.251	£7,519	£7,519
Utility	Impact of age excluded	Age-adjusted	£1,885	0.238	£7,913	£7,913
	Additive, general population-adjusted	Multiplicative, general population–adjusted cited as appropriate in TSD12	£1,885	0.235	£8,006	£8,425
Amputation as adverse event	Included	Excluded	£2,109	0.247	£8,538	£9,584
Non-elective inpatient costs	NHS Reference cost 2020/2021	2019/2020 cost inflated to 2020/2021	£2,046	0.251	£8,161	£10,068
HHF disutility period	1 month	2.75 months (11 weeks)	£1,885	0.256	£7,372	£9,844
Annual GP visits	23.14	6	£1,711	0.251	£6,826	£9,072
Length of hospitalisation for HHF	Weighted average of severe (53 days) and non-severe (13 days) case	13 days	£2,122	0.251	£8,466	£9,663
Treatment effect on UHFV event	Included	Excluded	£1,890	0.25	£7,522	£9,694
Treatment effect on CV and all-cause survival	Included	Excluded (direct effect)	£1,487	0.093	£16,004	£22,972

NICE ICERs presented are deterministic ICERs

CV, cardiovascular; HHF, hospitalisation for heart failure; UHFV, urgent heart failure visit

Dapagliflozin: EAG base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£7,980	4.427	£1,974	0.086	£22,972	-0.01	0.02
Soc	£6,006	4.342	-	-	-	-	-

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Dapagliflozin plus SoC	£7,963	4.413	£1,969	0.084	£23,411	-0.01	0.02
Soc	£5,994	4.329	-	-	-	-	-

NICE ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Dapagliflozin: EAG deterministic scenario analysis (1/2)

EAG's preferred assumptions:

- Utilities: multiplicative, age- and general-population adjusted
- Exclude amputation as an AE
- Non-elective inpatient cost: inflated 2019/2020
- HHF disutility period: 11 weeks
- Annual GP visits: 6
- Cost code for shorter HHF visit
- Exclude treatment effect on UHFV

Assumption: Impact of dapagliflozin on CV-related and all-cause deaths

Assumption: Cost associated with non-CV death

CV-related deaths	All-cause deaths	Cost associated with non-CV death	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Direct and indirect effect	Direct and indirect effect	Included	£9,694	0.12	0.15
		Excluded	£9,407	0.12	0.15
Direct and indirect effect	Indirect effect	Included	£24,137	-0.02	0.02
		Excluded	£22,321	-0.01	0.02
Indirect effect	Indirect effect	Included ★	£22,972	-0.01	0.02
		Excluded	£23,016	-0.01	0.02
No effect	No effect	Included	£35,636	-0.03	-0.01
		Excluded	£35,636	-0.03	-0.01

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; NHB, net health benefit; ICER, incremental cost-effectiveness ratio; inc., incremental; QALY, quality-adjusted life year

★ EAG base case

Dapagliflozin: EAG deterministic scenario analysis (2/2)

EAG scenario analyses (deterministic)

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus SoC	Incremental QALYs versus SoC	ICER (£) versus SoC
1	**EAG base case**	£1,974	0.086	£22,972
2	CV mortality survival using the Gompertz extrapolation	£1,826	0.072	£25,204

CV, cardiovascular; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Cost effectiveness results

Empagliflozin (ID3945)

NICE National Institute for Health and Care Excellence

Empagliflozin: Company base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Empagliflozin plus SoC	[redacted]	[redacted]	£1,407	0.10	£14,429	0.03	0.05
SoC	[redacted]	[redacted]	-	-	-	-	-

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
Empagliflozin plus SoC	[redacted]	[redacted]	£1,403	0.10	£14,564	0.03	0.05
SoC	[redacted]	[redacted]	-	-	-	-	-

NICE ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; SoC, standard of care

Empagliflozin: Company deterministic scenario analysis

Company scenario analyses (deterministic)

Scenario	Description	ICER (£/QALY)
Company base case		£14,429
One inflection point	Use the KCCQ quartile transition matrix used for months 4 to 8 in the model base case from month 4 to the end of the time horizon.	£22,000
Distribution for CV and all-cause mortality	Log-normal	£15,752
	Log-logistic	£15,030
	Exponential	£14,802
	Generalised	£14,473
	Gompertz	£17,553
Distribution for empagliflozin discontinuation	Weibull	£14,610
	Log-normal	£14, 808
	Log-logistic	£14,735
	Generalised gamma	£14,565
	Gompertz	£14,592
Utility: Age adjustment off	Use utility data as collected in the trial ([redacted]), without adjusting KCCQ 4 to be equal to UK general population utility.	£12,964
Non-CV death costs	Assuming that non-CV deaths incur the same costs as CV deaths.	£14,958

CV, cardiovascular; ICER, incremental cost-effectiveness ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; QALY, quality-adjusted life year

Empagliflozin: EAG deterministic base case results (1/2)

Assumptions in company and EAG base case

	Company base case	EAG base case	Inc. costs	Inc. QALYs	ICER with EAG assumptions (£/QALY)	Cumulative ICER with EAG assumptions (£/QALY)
Company base case			[redacted]	[redacted]	£14,429	£14,429
KCCS-CSS TPs	LOCF	Observed without imputation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect on CV and all-cause survival	**CV-related deaths:** Direct and indirect effect **All-cause deaths:** Indirect effect	**CV-related deaths:** Direct and indirect effect **All-cause:** No effect	[redacted]	[redacted]	[redacted]	[redacted]
Age-related utility decrements	Excluded	Included	[redacted]	[redacted]	[redacted]	[redacted]
Costing of HHF	Weighted mean from national FCEs for HHFs events	EB03E code (non-severe HHF)	[redacted]	[redacted]	[redacted]	[redacted]
Cost of CV death and sudden death	**CV death:** £4,295	**CV death:** £1,452 (cost of sudden death: £0)	[redacted]	[redacted]	[redacted]	[redacted]

The values for incremental costs and QALYs are for applied for each assumption separately (rather than cumulatively)

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CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; inc., incremental; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life

Empagliflozin: EAG deterministic base case results (2/2)

EAG presented a range of base case results, depending on the committee's preferred assumptions. All the EAGs base case ICERs are above £30,000/QALY

EAG's preferred assumptions:

- Observed KCCQ-CSS TPs data without imputation
- Age-related decrements from Ara and Brazier 2010
- EB03E code to cost HHF
- Unit cost for CV death of £1,452 (cost of sudden death of £0)

Assumption: Impact of empagliflozin on CV-related and all-cause deaths

Assumption: Duration of impact of HHF on QoL

		ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
CV-related deaths: Direct and indirect effect **All-cause deaths:** No effect	11 weeks	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]
CV-related deaths: No effect **All-cause deaths:** No effect	11 weeks	[redacted]	[redacted]	[redacted]
	6 months	[redacted]	[redacted]	[redacted]

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; inc., incremental; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life

Empagliflozin: EAG deterministic scenario analyses

Assumption: Impact of empagliflozin on CV-related and all-cause deaths

EAG's preferred assumptions:

- Observed KCCQ-CSS TPs data without imputation
- Age-related decrements from Ara and Brazier 2010
- EB03E code to cost HHF
- Unit cost for CV death of £1,452 (cost of sudden death of £0)
- **HHF disutility period: 11 weeks**

	ICER (£/QALY)	NHB at £20,000 /QALY	NHB at £30,000 /QALY
CV-related deaths: Direct and indirect effect **All-cause deaths:** Indirect effect	[redacted]	[redacted]	[redacted]
CV-related deaths: Direct and indirect effect **All-cause deaths :** No effect	[redacted]	[redacted]	[redacted]
CV-related deaths: Indirect effect **All-cause deaths:** Indirect effect	[redacted]	[redacted]	[redacted]
CV-related deaths: No effect **All-cause deaths :** No effect	[redacted]	[redacted]	[redacted]

CV, cardiovascular; EAG, evidence assessment group; HHF, hospitalisation for heart failure; ICER, incremental cost-effectiveness ratio; inc., incremental; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - clinical summary score; QALY, quality-adjusted life year; QoL, quality of life

Equality considerations

Equality considerations in ID1648 and ID3945 (HFmrEF and HFpEF):

- People in lower socioeconomic groups may have a higher risk of developing heart failure

Equality considerations in appraisals for HFrEF:

- People with black or South Asian background may have higher risk of developing heart failure
- Meta-analysis showed that SGLT2 inhibitors were more effective in people with a black or Asian family background
- Clinical experts said no reason to restrict SGLT2 inhibitors use based on age or ethnic background
- Committee noted that its recommendation applied to all people regardless of family background.

Dapagliflozin and empagliflozin: Other considerations

Requirement for HF specialist advice to initiate dapagliflozin and empagliflozin

Background

- SGLT2is are currently prescribed for HF for **reduced** ejection fraction in primary care, following advice of a HF specialist

Companies (empagliflozin, Boehringer Ingelheim) and (dapagliflozin, AstraZeneca)

- Socioeconomic deprivation is a strong risk factor for development of HF and adverse HF outcomes
- Inequality in access to specialist care in UK may contribute to this
- Broad prescribing of dapagliflozin empagliflozin in primary and secondary care could reduce health inequalities
- Requirement for HF specialist advice would delay access and contribute to resource constraints

Patient experts

- No need to refer for HF specialist advice when prescribing SGLT2i in primary care
- GPs are very familiar with SGLT2i as they are prescribed for T2DM, without specialist involvement
- Requirement for HF specialist advice increases waiting times and burden NHS, meaning patients suffer

Should initiation of dapagliflozin and empagliflozin require advice from a HF specialist, or can it be initiated in primary care?

HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2DM, type 2 diabetes mellitus

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Thank you.