Public observer – contains redacted data

NICE National Institute for Health and Care Excellence

Empagliflozin for treating chronic heart failure with reduced ejection fraction [ID3826]

Lead team presentation

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ERG: BMJ

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Company: Boehringer Ingelheim

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Heart failure with reduced ejection fraction (HFrEF)

Definition: Impaired ventricle filling and ejection of blood. The heart does not pump enough blood to meet body's demands

Reduced ejection fraction: ≤40% of blood pumped out of the left ventricle of the heart each time it beats (normal range 55% to 70%*)

Causes: structural or functional abnormalities of the heart – Ischaemic heart disease, hypertension and diabetes increase risk

Symptoms: difficulty breathing, fatigue, and ankle swelling, with significant quality of life impact

Classification: American Heart Association (AHA) 4 stages of heart failure

(A to D – high risk; structural without symptoms; structural with current symptoms; refractory)

or NYHA (New York Heart Association) classification: Class 1 to 4

1 is least severe and 4 most severe (Class 2 and above considered symptomatic)

Prevalence/ incidence: 920,000 people are estimated to live with HF in UK and 200,000 people are newly diagnosed with HF each year*. Most common cause of hospitalisation in people over 65 years

Treatment: chronic condition with no cure, treatment can control symptoms and prolong life

Survival: mortality estimates range between 14.4% to 26% (1-year) 48.5% to 68.1% (5-year)

*based on company estimates

Professional and patient organisation perspective

British Society for Heart Failure and Pumping Marvellous Foundation

Current treatment options:

- Access to specialist care can be limited and there are few options available in terms of drug class and effects
- More options give prescriber clinical choice but 1st and 2nd line therapies are oral medication
- Quantity of tablets can be overpowering, especially if several co-morbidities are included
- Side-effects tend to subside which allows prescribers to up-titrate and optimise
- Vast majority of patients would welcome more choice

Advantages of empagliflozin:

- Empagliflozin seems to have the same benefit as dapagliflozin. Feedback on dapagliflozin has been very positive with few side effects
- Empagliflozin is an important adjunct to the current set of treatments
- Empagliflozin shouldn't be a cause for concern for the patient, or in terms of medication adherence from the prescribing clinician
- Increased urination may cause initial inconvenience or potential discomfort and some may have urinary tract infections, which subside or stop when SGLT2i is removed
- Those with HFrEF and T2DM may need some adjustment of other glucose lowering medications SGLT2i represents a significant step-change in management of HFrEF

Other:

- No reason to withhold empagliflozin in people with any other shared characteristics
- Empagliflozin should not just be prescribed by a specialist but also by Primary Care GPs on the advice of a heart failure specialist

Key issues	Resolved?
Issue1: Generalisability of EMPEROR-R to UK clinical practice	
Issue 2: Difference in efficacy in Europe subgroup of EMPEROR-R	
Issue 3 a: Is dapagliflozin the most appropriate comparator? Issue 3 b: Uncertainty around efficacy of empagliflozin compared with dapagliflozin	
Issue 4: Modelling of patients' distribution across the health states	
Issue 5: Use of a Poisson model to estimate hospitalisation for heart failure	
Issue 6: Overestimation of hospitalisation for heart failure in the UK population	
Issue 7: Modelling of mortality	
Issue 8: Overestimation of mortality in the UK population	
Issue 9: Impact of hospitalisation for heart failure in patients' quality of life	
Issue 10: Quality of life regressions for the UK population	
Issue 11: Sex distribution underlying utility estimates	
Issue 12: Quality of life gains in EMPEROR-R	

Key: Model driver; Unknown impact; Small/moderate impact

Unresolved	Partially resolved	Resolved

Empagliflozin (Jardiance, Boehringer Ingleheim)

Description of technology	A reversible, SGLT2 inhibitor that reduces renal reabsorption of glucose and sodium and increases urinary excretion of glucose and moderates sodium excretion in the kidney
Marketing authorisation	Extension of indication issued 23rd July 2021: To include treatment of adult patients with heart failure and reduced ejection fraction
	Other indications: For treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance • in addition to other medicinal products for the treatment of diabetes
Dosage and administration	10 mg oral empagliflozin once daily
List price	28 tablets (10mg) is £36.59 (£1.31 per day) Annual cost = £477

Background

Comparators	NICE scope: • Individually optimised standard care without empagliflozin* • Dapagliflozin as an add-on to standard care
Company position and ERG critique	• Dapagliflozin is not a relevant comparator and not standard of care • ERGs clinical experts consider dapagliflozin is a key comparator
Clinical trial	EMPEROR-Reduced (phase III trial empagliflozin + standard care vs placebo n= 3730)
Key results	• Fewer people in empagliflozin group had a CV or HHF event compared with placebo (16 months follow-up) • Number of HHF- lower for empagliflozin than placebo group
Comparison with dapagliflozin	• Bucher ITC for EMPEROR-Reduced with DAPA-HF ** • Pooled meta-analysis of SGLT2Is vs placebo (Zannad *et al*. 2020)
Model structure	Markov cohort state-transition model, 5 health states (4 KCCQ-CSS quartiles and CV or non-CV death)

* Defined as ACE inhibitors / ARBs / sacubitril valsartan with beta-blockers and/or mineralocorticoid receptor antagonists
** DAPA-HF phase III trial compared dapagliflozin plus standard care with placebo, n= 4744
*** Includes pooled dapagliflozin and empagliflozin data vs placebo
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CV; cardiovascular, HHF; hospitalisations for heart failure, ITC; indirect treatment comparison, KCCQ-CSS; Kansas City Cardiomyopathy Questionnaire clinical summary score, SGLT2I; sodium-glucose co-transporter-2 inhibitor

Pathway from NICE guideline (NG106)

Seek specialist advise after ACEi or ARB and MRAs

Diagnosis of HFrEF by specialist in primary or secondary care

Mineralocorticoid receptor antagonist (MRA)

Angiotensin-converting-enzyme inhibitor (ACEi) + beta blocker

Intolerant of ACEi

Angiotensin II receptor blocker (ARB) + beta blockers

Company positioning: empagliflozin as an add-on to standard care

Dapagliflozin (TA679-published Feb 2021) *Add on to optimised standard care*

Worsening or continuing severe symptoms and:

Initiated by specialist

Ejection fraction ≤35%	Sinus rhythm, heart rate ≥75 bpm, ejection fraction ≤35%	Person of African-Caribbean family origin	Sinus rhythm
Add sacubitril valsartan (TA388) - Stop ACEi/ARBs	Add ivabradine (TA267)	Add hydralazine and nitrate	Add digoxin

ERG suggest empagliflozin initiated by specialist but could be in primary or secondary care
ERG notes TA679 (dapagliflozin) includes same population as that considered for empagliflozin
ERG and company agree sacubitril valsartan is a comparator of interest

Is dapagliflozin the most appropriate comparator?

Dapagliflozin was included as a comparator in final scope but company consider standard care alone is the most relevant comparator

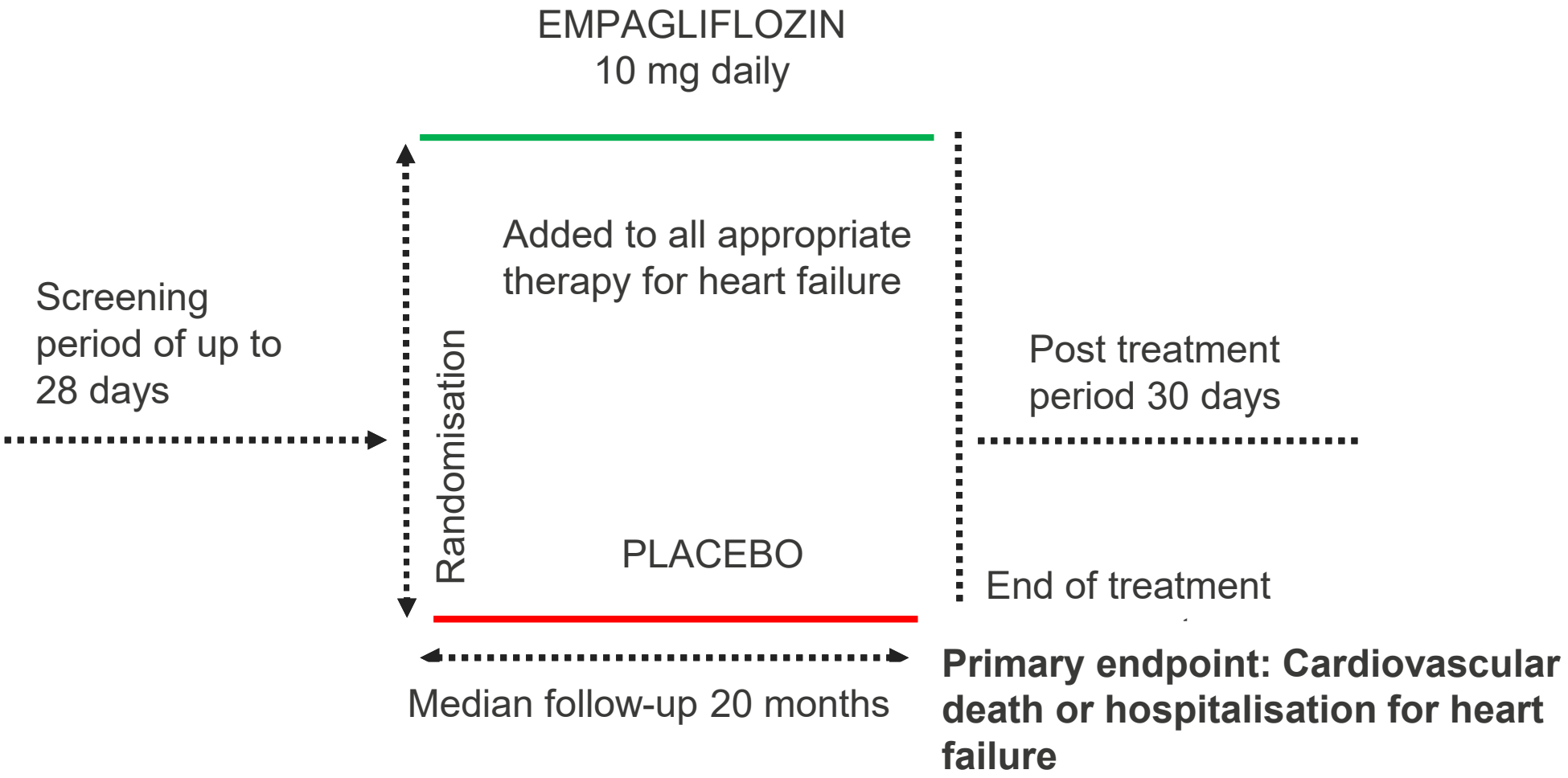
✓	✗
ERG's clinical experts suggest dapagliflozin uptake is increasing and it should be a key comparator.	**Company** suggest dapagliflozin is not standard of care in NHS. • Low market use in people with HF only (prescribing estimate xxxxx* it is mainly used in people with HF and T2DM and future use is speculative.
British Society for Heart Failure states current treatment includes dapagliflozin as add on to standard care	
Clinical expert opinion: dapagliflozin now in routine use for HFrEF and most appropriate treatment to compare with empagliflozin	

Is dapagliflozin the most appropriate comparator?

*based on market estimates to May 2021 ** both are SGLT2i's Abbreviations; ITC= Indirect treatment comparison T2DM= type 2 Diabetes Mellitus

Clinical Evidence

- **EMPEROR- Reduced trial design**



NICE Source Figure 5 in company submission

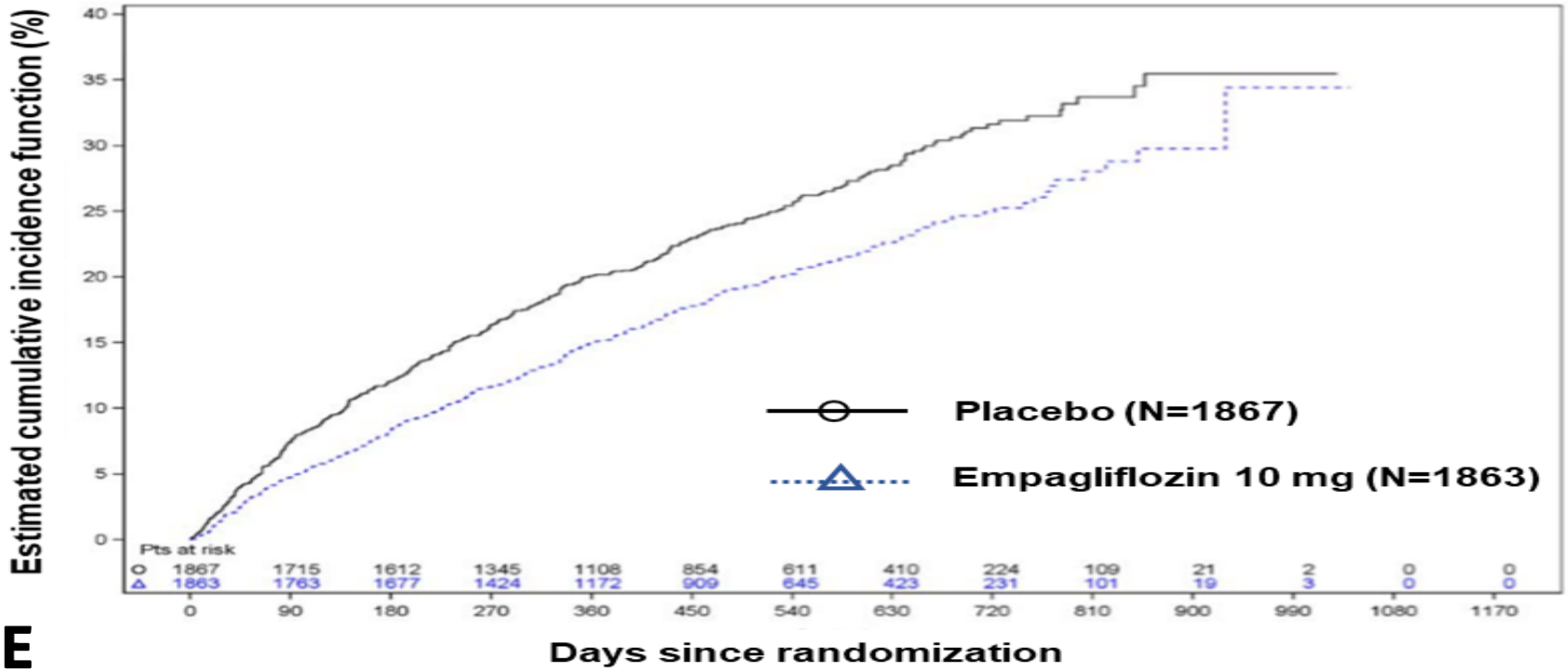
Clinical results for EMPEROR-Reduced

Primary outcome:

Combined risk of CV death or hospitalisation for heart failure – all randomised

Time to first event - combined risk of CV death or hospitalisation for heart failure		
Median follow-up 16 months	**Number of events**	**Combined risk HR (95% CI)**
Empagliflozin (n= 1863)	361 (19.4%)	0.75; 0.65 to 0.86; p<0.0001
Placebo (n=1867)	462 (24.7%)	

Estimated cumulative incidence function: Time to first adjudicated CV death or HHF event



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Clinical results for indirect treatment comparison

Endpoint: relative effect measure	EMPEROR-R:	DAPA-HF:	Bucher ITC:
Time to first event of adjudicated CV death or adjudicated HHF: HR (95% CI)	0.75 (0.65 to 0.86)	0.75 (0.65 to 0.85)	[redacted]
Time to first adjudicated CV death or adjudicated HHF (EMPEROR-Reduced) vs Time to first worsening of heart failure or CV death (DAPA-HF): HR (95% CI)	0.75(0.65, 0.86)	0.74 (0.65, 0.85)	[redacted]
Time to first adjudicated HHF: HR (95% CI)	0.69 (0.59 to 0.81)	0.70 (0.59 to 0.83)	[redacted]
Time to adjudicated CV death: HR (95% CI)	0.92 (0.75 to 1.12)	0.82 (0.69 to 0.98)	[redacted]
Time to all-cause mortality: HR (95% CI)	0.92 (0.77 to 1.1)	0.83 (0.71 to 0.97)	[redacted]
Occurrence of adjudicated HHF (first and recurrent): HR (95% CI)	0.70 (0.58, 0.85)	0.71 (0.61, 0.82)	[redacted]
Occurrence of adjudicated HHF (first and recurrent): RR (95% CI)	0.76 (0.65, 0.89)	0.75 (0.65, 0.88)	[redacted]
Worsening renal function (as defined in DAPA-HF): HR (95% CI)	0.52 (0.29 to 0.92)	0.71 (0.44 to 1.16)	[redacted]
Change in KCCQ total symptom score at 8 months/7.4 months: MD (SE/95% CI)	1.6 (0.7)	2.8 (0.5)	[redacted]

Abbreviations: CV, cardiovascular; HHF, hospitalization for heart failure; HR hazard ration; CI, confidence interval; RR, risk ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Comparison of baseline characteristics

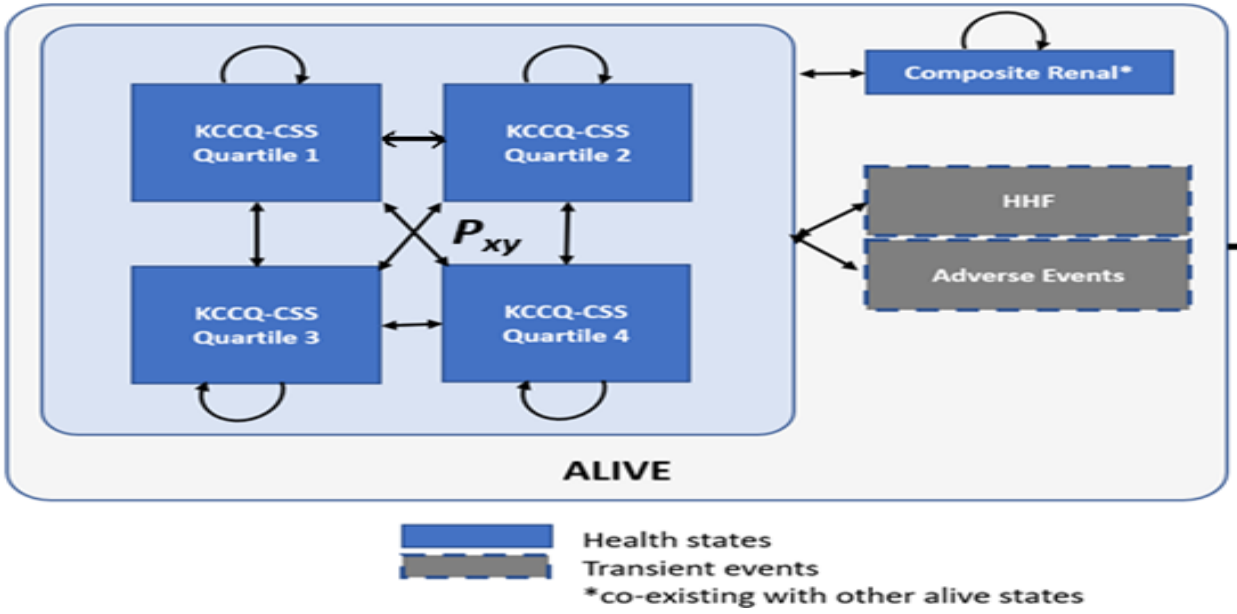
	EMPEROR-Reduced		DAPA-HF	
Treatment (N)	Empagliflozin (N = 1,863)	Placebo (N = 1,867)	Dapagliflozin (N = 2,373)	Placebo (N = 2,371)
Age, mean (SD)	67.2 (10.8)	66.5 (11.2)	66.2 (11.0)	66.5 (10.8)
Female sex, n (%)	437 (23.5)	456 (24.4)	564 (23.8)	545 (23.0)
North America, n (%)	212 (11.4)	213 (11.4)	335 (14.1)	342 (14.4)
South/Latin America, n (%)	641 (34.4)	645 (34.5)	401 (16.9)	416 (17.5)
Europe, n (%)	676 (36.3)	677 (36.3)	1,094 (46.1)	1,060 (44.7)
Asia Pacific, n (%)	248 (13.3)	245 (13.1)	543 (22.9)	553 (23.3)
NYHA I, n (%)	0	0	0	0
NYHA II, n (%)*	**1399 (75.1)**	**1401 (75.0)**	**1,606 (67.7)**	**1,597 (67.4)**
NYHA III, n (%)*	**455 (24.4)**	**455 (24.4)**	**747 (31.5)**	**751 (31.7)**
NYHA IV, n (%)	9 (0.5)	11 (0.6)	20 (0.8)	23 (1.0)
LVEF – %, mean (SD)*	27.7 (6.0)	27.2 (6.1)	31.2 (6.7)	30.9 (6.9)
NT-pro-BNP – pg/ml, median (IQR)*	**1,887 (1077, 3429)**	**1,926 (1153, 3525)**	**1,428 (857, 2,655)**	**1,446 (857, 2,641)**
Ischaemic HF, n (%)	983 (52.8)	946 (50.7)	1316 (55.5)	1358 (57.3)
HHF, n (%)*	**577 (31.0)**	**574 (30.7)**	**1,124 (47.4)**	**1,127 (47.5)**
Atrial fibrillation, n (%)	664 (35.6)	705 (37.8)	916 (38.6)	902 (38.0)
Diabetes mellitus, n (%)	927 (49.8)	929 (49.8)	993 (41.8)	990 (41.8)
eGFR – ml/min/1.73m^2 Mean (SD)	61.8 (21.7)	62.2 (21.5)	66.0 (19.6)	65.5 (19.3)

*Indicates baseline characteristics where ERG noted variations between trials.
In EMPEROR-R number of HHF based on previous 12 months, in DAPA-HF there was no time limit on prior HHF
ERG consider LVEF and NT-pro-BNP suggest EMPEROR-R patients were likely sicker than DAPA-HF and at increased risk of HHF and mortality

Company model overview

Company model:

- Cohort state transition model with lifetime horizon of 33 years
- States represents Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)*
- The 4 KCCQ-CSS health states represent the different levels of disease severity experienced by patients – the higher the score the better the health status.
- Uses quartiles corresponding to KCCQ-CSS sores



Technology is modelled to affect costs:

- Higher cost for treatment
- ↓ probability of being hospitalised for heart failure
- ↓ probability of patients receiving dialysis

Technology is modelled to affect QALYs by:

-↑ proportion of patients who remain in better KCCQ-CSS states – leads to better survival / lower hospitalisation rates

↓ patients hospitalised for heart failure

* a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life

Outstanding issues

Key issues unresolved after technical engagement	Impact
Issue 1: Trial generalisability • Is the EMPEROR-R trial generalisable to UK clinical practice?	
If dapagliflozin is the most appropriate comparator	
Issue 3: Efficacy of empagliflozin compared with dapagliflozin • What is the most appropriate method to compare empagliflozin with dapagliflozin?	
If dapagliflozin is not an appropriate comparator	
Issue 5 Use of a Poisson model to estimate HHF • Does the company's updated analysis accurately reflect the number of hospitalisations for heart failure in UK clinical practice?	
Issue 6: Overestimation of hospitalisations for heart failure in UK population • Does the company's updated analysis accurately reflect the number of hospitalisations for heart failure in UK clinical practice?	
Issue 9: Impact of HHF in patients quality of life • Should a disutility for having a hospitalisation for heart failure be used? If so, for how long should it be applied?	

Key: Model driver Unknown impact; Small/moderate impact

Issues resolved at Technical Engagement

Issue	Summary	Technical team consideration
2	ERG suggest there may be a difference between Europe subgroup and ITT outcome data in EMPEROR-R	Company provide additional data for EUROPE subgroup. Tech team and ERG satisfied issue is resolved
4	ERG request additional data to validate company assumptions on patients transition across health states	Company provided requested information. Tech team and ERG satisfied issue resolved
7	ERG consider assumption of constant treatment effect of empagliflozin over SoC is unsubstantiated for all-cause and CV-related death	Company adopted new base case (no direct survival benefit of empagliflozin over SoC) - ERG preferred updated analyses
8	ERG considered CV-deaths in SoC arm of company model were overestimated. Suggested KM curves were adjusted to reflect mortality curves in PULSE	Company calibrated mortality data based on joint regression for EMPEROR-R and PULSE. ERG noted small ICER decrease
10	Company used baseline characteristics from ≥ 65 years subgroup in QoL regression analysis but coefficients for predictors were same as ITT	Company re-estimated regression using subgroup data. ERG noted result on ICER was negligible
11	ERG noted utility values of KCCQ-CSS quartile 4 health state did not reflect sex distribution in EMPEROR-R or PULSE	Company updated utility values based on gender distribution in EMPEROR-R and PULSE. ERG agrees this had little impact
12	ERG concerned there may be a difference in QOL reported in EMPEROR-R and results generated by company's model	Company provided additional scenario analyses at ERG request

Issue 1: Generalisability to older HFrEF population

Background:
- EMPEROR-R ITT population (mean age 67 years) had more severe HFrEF than expected in UK clinical practice
- Age subgroup analysis suggest [redacted]

Company:
- Baseline data = ITT and ≥65 years subgroup are broadly comparable
- Low sample size in ≥65 years subgroup would decrease certainty in CE estimates and increase disparity access across ethnic and socio-economic groups.
- Large amounts of missing data in PULSE make it impossible to characterise typical' UK patient

Consultee- AstraZeneca:
EMPEROR-R has a more severe population so may not be generalisable to UK clinical practice

ERG critique:
- Consider ≥65 years age subgroup important- HFrEF data in PULSE is reasonable
- EMPEROR-R population approx.10 yrs younger than UK clinical practice
- Some baseline differences and difference in efficacy in ≥65 years subgroup compared to ITT
- Subgroups – should be interpreted with caution - EMPEROR-R was not powered to detect differences

NB: ERG economic analyses carried out using ITT (trial) and ≥65 years subgroup (UK population)

Is the EMPEROR-R trial generalisable to UK clinical practice?

HFrEF: Heart failure with reduced ejection fraction

Issue 3: Empagliflozin compared with dapagliflozin (1)

Background:

- ERG considered results of the Bucher ITC to be [redacted] and assumption of [redacted] was not robust
- Results of ITC showed [redacted] for any outcome however a trend with empaglifozin compared to dapagliflozin suggests:
  - [redacted]
  - [redacted]
- ERG requested an incremental analysis of empagliflozin vs dapagliflozin

Company

- Limited evidence dapagliflozin is standard of care, and relevant comparator. Cost comparison most appropriate
- Bucher ITC showed [redacted]
- Previous TAs suggest a cost comparison is reasonable: TA679 (dapagliflozin for HFrEF), committee accepted equal efficacy dapagliflozin vs sacubitril/valsartan
- Suggest an assumption of [redacted] and safety of SGLT2 is largely accepted by the clinical community
- Provided cost-utility comparison but consider it conceptually flawed – extrapolates uncertainty
- Provided a naïve comparison for CV mortality using KM from EMPEROR-R and DAPA-HF

Issue 3: Empagliflozin compared with dapagliflozin (2)

Stakeholder responses- AstraZeneca:

- Clinical effectiveness uncertain - it is not appropriate to disregard differential effects on key end-points from the trials and assume equivalent efficacy
- Agree company should generate an ICER for empagliflozin versus dapagliflozin

ERG TE response:

- Agree company should generate an ICER for empagliflozin versus dapagliflozin
- Noted significant uncertainty around efficacy of empagliflozin but does not consider company model has captured magnitude of the uncertainty
- The company's analysis included a benefit associated with empagliflozin for HHF and renal outcomes
- ERG's preference is to include the Bucher HRs on mortality for empagliflozin vs dapagliflozin although the ERG appreciates that none of the results from the Bucher ITC are xxxxxxxxxxx xxxxxxxxxxxx
- Assuming equivalence results in the two treatments having identical costs and benefits
- ERG exploratory analyses – Corrected hazard ratios for renal outcome used in company base case and explored impact of adding different hazard ratios from Bucher ITC on ICER for ITT population and > 65 year subgroup
  - key drivers are inclusion of survival benefit for dapagliflozin and improvements in renal function for empagliflozin.

What is the most appropriate method to compare empagliflozin with dapagliflozin?

Company and ERG assumptions for empagliflozin vs dapagliflozin

Company Base case*
Different scenarios assuming: • no survival benefit of empagliflozin over dapagliflozin • HHF benefit for empagliflozin • renal benefit for empagliflozin
ERG additional analyses**
Different scenarios assuming: • equal effectiveness between treatments in all outcomes • survival benefit for dapagliflozin • survival benefit for dapagliflozin + HHF benefit for empagliflozin • survival benefit for dapagliflozin + HHF benefit for empagliflozin + renal benefit for empagliflozin

*Company population based on EMPEROR-R ITT; ERG carried out separate analyses on ITT (trial population) and ≥65 years subgroup (UK population)
** ERG carried out additional analyses based on results of the Bucher ITC and corrected the HRs used in the company base case
HHF= hospitalisations for heart failure

Cost effectiveness results (1)

ERG Incremental changes to ICER for empagliflozin vs dapagliflozin in ITT population

		Empagliflozin	Dapagliflozin	Inc value
Company's base case corrected (assuming HHF benefit for empagliflozin + renal benefit for empagliflozin)				
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	Dominant
0 Assuming equal effectiveness between treatments in all outcomes				
	Total costs	[redacted]	[redacted]	£0
	QALYs	[redacted]	[redacted]	0.00
	ICER (£/QALY)	-	-	-
1 Assuming survival benefit for dapagliflozin				
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]*
1+2 Assuming survival benefit for dapagliflozin + HHF benefit for empagliflozin				
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]*
1+2+3 survival benefit for dapagliflozin + HHF benefit for empagliflozin + renal benefit for empagliflozin				
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]*

Abbreviations: HHF; hospitalisations for heart failure, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

***South-west quadrant ICERs - Less costly and less effective ICER= <£20,000 per QALY**

Cost effectiveness results (2)

ERG Incremental changes to ICER for empagliflozin vs dapagliflozin in >65 yr subgroup

	Results per patient	Empagliflozin	Dapagliflozin	Inc value
Company's base case corrected (HHF benefit for empagliflozin + renal benefit for empagliflozin)				
	Total costs	xxxxxxx	£18,003	xxxxx
	QALYs	xxxx	xxxx	xxxx
	ICER (£/QALY)	x	x	Dominant
0 Assuming equal effectiveness between treatments in all outcomes				
	Total costs	xxxxxxx	xxxxxxx	£0
	QALYs	xxxx	xxxx	0.00
	ICER (£/QALY)	-	-	-
1 Assuming survival benefit for dapagliflozin				
	Total costs	xxxxxxx	xxxxxxx	xxxxx
	QALYs	xxxx	xxxx	xxxxx
	ICER (£/QALY)			xxxxx*
1+2 Assuming survival benefit for dapagliflozin + Assuming HHF benefit for empagliflozin				
	Total costs	xxxxxxx	xxxxxxx	xxxxx
	QALYs	xxxx	xxxx	xxxxx
	ICER (£/QALY)			xxxxx*
1+2+3 survival benefit for dapagliflozin + HHF benefit for empagliflozin + renal benefit for empagliflozin				
	Total costs	xxxxxxx	xxxxxxx	xxxxx
	QALYs	xxxx	xxxx	xxxxx
	ICER (£/QALY)			xxxxx*

Abbreviations: HHF; hospitalisations for heart failure, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year* South-west quadrant ICERs - Less costly and less effective ICER= <£20,000 per QALY

If dapagliflozin is not an appropriate comparator

Issue 5: Use of a Poisson model to estimate HHF

Background

- Company used count data from EMPEROR-R to model number of hospitalisation for heart failure (HHF). Poisson model assumed HHF rate is constant over time
- ERG unclear if HHFs are accurately estimated and suggest a scenario analyses using Kaplan-Meier data from EMPEROR-R

Company:

- Assumption overall rate of HHF remains constant over lifetime of the model is consistent with TA267 (ivabradine), TA388 (sacubitril valsartan), TA679 (dapagliflozin)
- ERG approach uses total number of HHF events, and requires transformation of Kaplan-Meier HHF data into count data – showed rate in hospitalisations declined over time. This is contra to clinical opinion- suggest hospitalisations would increase
- Provided scenario to allow HHF rates to increase over time
- findings supported the use of a fitted Poisson model which assumed a constant rate of hospitalisation, while allowing the rate to increase as patients progress over time through inclusion of time-varying KCCQ-CSS as a predictor
- Scenario reduced ICER from £4,717 to £4,492 due to higher reduction in number of HHFs

ERG critique:

- Acknowledges company approach accurately reproduces number of HHFs observed in the trial over 18 months and agrees that increasing rates of HHF overall in the model benefits empagliflozin
- Maintains view using Kaplan- Meier HHF data from EMPEROR-R would allow company to estimate long-term HHF using observed data
- uncertain if HHFs are accurately estimated in long-term model (see next slide)

Issue 5: Use of a Poisson model to estimate HHF

ERG preliminary analysis: Time to 1st and 2nd HHF event (ITT population EMPEROR-R)

* Based on people who had a first HHF event, not total randomised population.

- **ERG** – KM curves suggest empagliflozin delayed time to 1st HHF vs standard of care
- Although time to 2nd HHF was quicker for both treatments, the order swapped (fewer people having standard care had a HHF at year 1 and year 2 vs empagliflozin) % having 2nd HHF in EMPEROR-R= empagliflozin 35%; SoC 33%
- Company analysis did not capture this change in trend for time to 1st and 2nd HHF - If 1st and 2nd events were separated in model, it is likely the benefit associated with empagliflozin on HHF would reduce

Should the number of hospitalisations for heart-failure be modelled using Kaplan-Meier data from EMPEROR-Reduced?

Non-randomised clinical evidence: PULSE Used in validation of company model

- PULSE is a non-interventional cohort study based on data from the UK CPRD and linked to the HES inpatient and ONS mortality data
- Company used evidence from PULSE to check the external validity of their economic model and to inform the modelling of mortality
- ERG notes PULSE show a [redacted] rate of HHF compared to with SoC in EMPEROR-R (age and sex adjusted HHF rate of [redacted] patient years in PULSE compared to [redacted] patient years in the placebo arm of EMPEORER-R).
- KCCQ-CSS scores were not collected in PULSE the company's model structure relies on KCCQ-CSS scores to estimate HHF. The company reported that they could not include the data from PULSE in their economic model

CPRD= Clinical Practice Research Datalink, HES= Hospital Episodes Statistics, ONS= Office for National Statistics

Issue 6: Overestimation of HHF in UK population

Background

- Company used hospitalisations for heart failure (HHF) rate from ITT in EMPEROR-R to model time to HHF (see issue 5)
- ERG note HHF rates higher in EMPEROR-R compared to PULSE- suggest company analysis overestimated HHF rates (see issue 1)
- ERG suggest scenario using Kaplan-Meier data for ≥65 years subgroup to model time to HHF

Company:

- Using ≥65 years subgroup will introduce uncertainty (represents 63% of EMPEROR-R data)
- Equity issues (younger population may belong to lower socio-economic/ ethnic group)
- Differences in HHF rates in EMPEROR-R and PULSE caused by inaccurate reporting not differences in patient characteristics
- Carried out scenario analysis using 0.43 rate-ratio adjustment factor to calibrate model to rate observed in PULSE **(ICER increased £4,717 to £7,000/QALY gained empagliflozin vs SoC)**

ERG critique:

- Company scenario analysis more accurately reproduces number of HHFs observed in the first 3 years of PULSE. But ERG uncertain if HHFs are accurately estimated in long-term model for UK relevant population
- Company did not provide HHF Kaplan-Meier data for ≥65 subgroup so ERG could not carry out equivalent analysis previously done for ITT

Does the company's updated analysis accurately reflect the number of hospitalisations for heart failure in UK clinical practice?

Issue 9:Impact of HHF on quality of life

Background

- Company assumed all HHFs in model last 1 year but ERG suggest unlikely to have that duration. Considers impact of HHF on patients' quality of life is overestimated in the model.
- ERG request company provide as much detail as possible on duration of HHF in EMPEROR-R to ascertain extent of overestimation and suggest weighted disutility value could be applied based on proportion of patients in EMPEROR-R who were hospitalised for 1, 2; and 8 months

Company:

- Clarified utility equation included indicators for time since hospitalisation rather than duration

Stakeholder responses- AstraZeneca:

- Company used an annual disutility of xxxxx But unlikely reduction will last that long
- Inappropriate to use an annual disutility and recommend considering the impact of a smaller disutility in the model

ERG critique:

- The second biggest driver of QALY gains comes from reduction in HHF events associated with empagliflozin
- ERG scenario analysis using disutility of 0.213,(based on TA388 sacubitril valsartan for HFrEF) and assumed that HHFs impact patients' QoL over 3 months
  (increased ICER from £4,999 to £5,211 for trial and from £7,270 to £7,460 in UK population)
  - In TA679 assumed HHFs impact patients' QoL over 12 months, with disutility of 0.32 per event
- ERG recommends committee validates company assumption that 100% of HHFs impact patients' QoL for 12 months after the event.

Should a disutility be applied? If so, for how long should it be applied?

Company and ERG model assumptions

1. Company Base case*	1. ERG additional analyses*
1. 74% have lifelong treatment 2. Utility adjustments from Sullivan (2011) 3. Proportion of SoC treatments based on baseline distribution in EMPEROR-R 4. Unit cost of CV death based on Alva et al (2015) 5. Unit costs of dialysis from Kerr et al (2012) 6. HHFs impact on QoL for 12 months (key issue 9)	1. 84% have lifelong treatment 2. Relative utility adjustment and age-related decrements from Ara and Brazier (2010) 3. Numbers having ACEi and ARNi reflects ERG experts' opinion 4. Unit cost for CV death = £1,582 5. ERG-calculated annual cost of dialysis (3 weekly sessions) = £23,088 6. HHFs impact on QoL over 3 months, and a disutility of 0.213 (key issue 9)

ERG further analyses applied to either trial or UK population**	Population
a) Using Weibull survival model and assuming no direct or indirect survival benefit of empagliflozin over standard care (issue 7) b) KCCQ-CSS quartiles proportions are equal at year 1 + no survival benefit for empagliflozin + transition probabilities between KCCQ-CSS quartiles for on and off treatment are the same after year 1 (issue 4)	Trial & UK Trial & UK
c) Using company's HR to adjust survival to reflect PULSE survival (issue 8) d) Using company's adjusted Poisson model to the PULSE HHF data (issue 5) e) Using 0.723 utility value for the KCCQ-CSS quartile state (issue 11)	UK only

*Company population based on EMPEROR-R ITT; ERG carried out separate analyses on ITT (trial population) and ≥65 years subgroup (UK population)

** ERG carried out further analyses and applied this to either trial, UK or both populations

Assumptions 1 to 5 were discussed in the original ERG report but not during Technical Engagement

ERG's scenario analysis results – Trial population		Inc costs	Inc QALYs	ICER
0	**Company's base case post TE**	**£722**	**0.14**	**£4,999**
1	84% of patients receive lifelong treatment with empagliflozin	£1,157	0.21	£5,465
2	Use relative utility adjustment and the age-related decrements from Ara	£722	0.14	£5,208
3	Replacing the proportion of UK patients who receive ACEi and ARNi in the model to reflect the ERG's clinical experts' opinion	£710	0.14	£4,912
4	Using a unit cost for CV death in the model of £1,582	£733	0.14	£5,072
5	Applying the ERG-calculated annual cost of dialysis (assuming 3 weekly sessions) of £23,088	£815	0.14	£5,640
6	Assuming that HHFs impact patients' QoL over 3 months, with a disutility of 0.213.	£722	0.14	£5,211
a	Using the company's updated Weibull survival model and assuming that empagliflozin has no direct or indirect survival benefit over SoC.	£393	0.08	£4,777
b	Assuming proportion patients in KCCQ-CSS quartiles under treatment arm is equal to proportions in the placebo arm at 1 year + assuming no survival benefit for empagliflozin + assuming the TPS between KCCQ-CSS quartiles for patients on treatment are same as those for patients off treatment (after year 1).	£446	0.05	£8,224
	Combined (1-6b) Assuming HHF QOL impacted 3 months+disut	£926	0.08	£12,234

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

ERG's scenario results UK population (≥ 65 years)		Inc Costs	Inc QALYs	ICER
0	Company's base case post TE.	£971	0.13	£7,270
1	84% of patients receive lifelong treatment with empagliflozin.	£1,490	0.18	£8,089
2	Relative utility adjustment and age-related decrements from Ara	£971	0.13	£7,620
3	Proportion who receive ACEi and ARNi reflect ERG's expert opinion.	£958	0.13	£7,173
4	Using a unit cost for CV death in the model of £1,582.	£984	0.13	£7,368
5	ERG-calculated annual cost of dialysis of £23,088.	£1,051	0.13	£7,872
6	HHFs impact patients' QoL over 3 months, with a disutility of 0.213.	£971	0.13	£7,460
c	Using company's updated Weibull survival model assuming empagliflozin has no direct or indirect survival benefit over SoC.	£607	0.06	£9,780
d	Using company's HR to adjust the survival to reflect PULSE survival.	£974	0.15	£6,708
e	Using company's adjusted Poisson model to the PULSE HHF data.	£1,152	0.12	£9,678
f	Using 0.723 utility value for the KCCQ-CSS quartile state	£971	0.13	£7,601
g	Assuming proportion patients in the KCCQ-CSS quartiles under treatment arm is equal to proportions in the placebo arm at 1 year + assuming no survival benefit for empagliflozin (using the HR to adjust the survival to reflect PULSE) + assuming the TPS between KCCQ-CSS quartiles for patients on treatment are same as those for patients off treatment (after year 1).	£636	0.04	£15,647
	Combined 1to 6 c, d, e	£1748	0.07	£24,663

Other considerations

Innovation

- There is a high unmet need for an effective treatment that improves HFrEF outcomes, symptoms and QoL among high-risk patients with CRM comorbidities
- empagliflozin offers a step change in the management of HFrEF within the NHS

Equality

- Company suggest socio-economic deprivation is a strong risk factor for the development of HF and adverse HF outcomes
  - People in the lowest socio-economic group are 1.61 times more likely to experience incident HF than the most affluent individuals and do so, on average, at a 3.5 years younger age with a greater comorbidity burden at time of HF symptom onset
  - Socio-economic status has an impact on access to secondary care in the UK, and subsequently access to HF treatments

CRM= cardio-renal-metabolic

- **Is empagliflozin an innovative treatment for HFrEF?**
- **Are there any additional benefits with empagliflozin that have not been captured adequately in the economic model?**
- **Are there any equality issues relevant to this appraisal?**